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Anticoagulant Therapy: Clinical Experience With Acenocoumarin (Sintrom) and Other Coumarin Derivatives

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A wealth of clinical experience has been gained in the control of thromboembolic disorders with coumarin derivatives. It is the purpose of this report to describe the treatment of 382 patients with these anticoagulants, with special reference to 305 patients treated with acenocoumarin (Sintrom) over a four-year period, many of them on long-term therapy.

Acenocoumarin is a relatively new coumarin derivative which has been made commercially available only recently. Its potency is 25 times that of phenylindanedione, and 40 times that of ethyl biscoumacetate.

Acenocoumarin has been found to possess certain advantages in clinical use.[1-7] Its duration of effect is substantially shorter than that of bishydroxycoumarin, but is sufficiently long so that patients may be maintained satisfactorily on a single daily dose. Satisfactory therapeutic hypoprothrombinemia can be achieved in two to three days with acenocoumarin and can be easily reversed when it is necessary to increase the prothrombin level to its normal range, by discontinuing the drug. The administration of vitamin K is usually unnecessary.

MATERIALS AND METHODS

Coronary artery disease in 287 patients accounted for most of the experience reported in this study, as shown in Table I. In this category were included patients with progressive coronary insufficiency as well as patients with frank myocardial infarction; arterial emboli were present in 14 of these patients when anticoagulant therapy was initiated. Other cardiovascular diseases accounted for the use of anticoagulants in the remaining 95 patients: 40 patients treated for episodes of arterial embolism, 30 patients with atrial fibrillation treated prophylactically during quinidine therapy, 16 patients in congestive heart failure in whom there was a history of thromboembolic accident, 6 patients with thrombophlebitis, and 3 patients in whom atrial thrombosis was observed during mitral commissurotomy.

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While acenocoumarin was the anticoagulant employed most commonly during this study, bishydroxycoumarin (Dicumarol) and ethyl biscoumacetate (Tromexan) were used in a substantial number of cases, as shown in Table I, and served as a basis for the evaluation of the newer agent.

The quick prothrombin time test was used in all cases to measure the adequacy of therapeutic control. Normal values were usually about 13 seconds, and therapeutic levels of hypoprothrombinemia were considered to be attained when the prothrombin time was about 25 seconds (15 to 30 per cent of normal).

Care was taken throughout the study to assure the reliability of laboratory measurements. Standard conditions were established for all determinations, and all work was carried out under the direction of the same individuals. It is believed that these procedures have minimized the incidence of laboratory errors.

TABLE I. PATIENTS RECEIVING ANTICOAGULANT THERAPY

ANTICOAGULANT	NUMBER OF PATIENTS			DURATION OF THERAPY (PATIENT-MONTHS)
	TOTAL	CORONARY ARTERY DISEASE	OTHER CARDIOVASCULAR DISEASE	
Acenocoumarin	305	240	65	604
Bishydroxycoumarin	40	25	15	29
Ethyl biscoumacetate	37	22	15	17
Total	382	287	95	650

A continuing record was kept for each patient, in which the prothrombin times were recorded graphically. This card was also used to note dosage changes and any complications that occurred.

During the four years of the study, our experience with these anticoagulants has included a total of 650 patient-months of therapy, of which 604 patient-months represent treatment with acenocoumarin. Bishydroxycoumarin and ethyl biscoumacetate account for the rest of the treatment, as indicated in Table I.

RESULTS

The dosage requirements of acenocoumarin differ substantially from those of other coumarin derivatives, as summarized in Table II. Using bishydroxycoumarin, therapeutic levels of hypoprothrombinemia could be established after 3 to 6 days with a loading dose averaging 445 mg. during the first 48 hours, followed by a maintenance dose averaging 79 mg. daily. Using instead the short-acting agent ethyl biscoumacetate, equivalent results were obtained with a loading dose of 1,280 mg. during the first 24 hours, and a daily maintenance dose averaging 387 mg.

Acenocoumarin is far more potent than the other agents on the basis of weight, and is intermediate between them in the time required for induction. In patients with initially normal prothrombin time, therapeutic levels of hypoprothrombinemia can be attained in 2 to 3 days with loading doses of 11 to 25 mg. After the induction period, an average dose of 3.6 mg. daily has maintained the prothrombin times of our patients at satisfactory therapeutic levels. However, when the prothrombin time is prolonged to begin with, a much lower dose

is required for induction. We have found that induction can be accomplished most satisfactorily in such cases with half the usual loading dose, as indicated in Table III.

In addition, it has been observed that smaller dosages of acenocoumarin are required in patients with cardiac or renal insufficiency. Induction of therapy in 43 patients with right heart failure was accomplished, on the average, with 16 mg. of acenocoumarin over 48 hours, and a maintenance dose of 3.1 mg. thereafter. Patients in uremia required no reduction of the loading dose, but were maintained satisfactorily on doses averaging 2.7 mg. The decreased requirement in this instance presumably resulted from accumulation of acenocoumarin due to impaired renal function.

TABLE II. DOSAGE SCHEDULES EMPLOYED

ANTICOAGULANT	INDUCTION TIME (HOURS)	INDUCTION DOSE	MAINTENANCE DOSE
Acenocoumarin	18–60	11–25 mg.	3.6 mg.
Bishydroxycoumarin	48	445 mg.	79 mg.
Ethyl biscoumacetate	24	1,280 mg.	387 mg.

TABLE III. INDUCTION DOSAGE OF ACENOCOUMARIN

INITIAL PROTHROMBIN TIME	REQUIRED INDUCTION DOSAGE		
	18 HR.	36 HR.	60 HR.
Normal	11 mg.	22 mg.	25 mg.
Prolonged	5.4 mg.	12 mg.	16 mg.

Because the initial dosage requirements established here for acenocoumarin differ appreciably from those reported previously, the effect of increasing the loading dose was studied. During the first 24 hours varying amounts of acenocoumarin up to 24 mg. were administered to 65 patients, and their 24-hour prothrombin times compared. It was found that doses of 8 to 12 mg. reduced the prothrombin values to 50 to 60 per cent of normal, while larger doses caused no further reduction. It seems useless therefore to give much larger doses, as has been recommended. In our experience, the optimum dose has been 12 to 16 mg. on the first day, followed bv 8 mg. on the second day.

Following the period of induction, we have observed that very stable levels of hypoprothrombinemia may be maintained with acenocoumarin over an indefinite period of time. This stability simplifies its use, particularly in long-term therapy, and has permitted us to control patients adequately with prothrombin times determined only once a month, or even in certain cases once every other month.

Acenocoumarin is comparable to bishydroxycoumarin in its stability of action. We have found that with either agent the prothrombin levels remain stable in about 90 per cent of the patients. On the other hand, marked variations of prothrombin time have occurred on several occasions with the use of ethyl biscoumacetate. In fact, it has been impossible to maintain the prothrombin time consistently within the therapeutic range in 20 out of 37 patients in which this agent was used.

When the normal clotting mechanism of the blood is artificially altered, as in anticoagulant therapy, it is most important to be able to restore the prothrombin time quickly when necessary. While vitamin K preparations are available for this purpose, it is usually sufficient with ethyl biscoumacetate or acenocoumarin simply to discontinue the drug. Normal values are attained in this way in about 1 day with ethyl biscoumacetate, and in about 2 days with acenocoumarin. Bishydroxycoumarin, because of its longer action, usually requires administration of vitamin K to correct the tendency toward hemorrahge.

Table IV illustrates the hemorrhagic complications observed during this study. Because acenocoumarin was employed more extensively than the other agents, we have calculated the incidence of hemorrhage on each anticoagulant in terms of the number of hemorrhagic episodes per unit time of therapy, showing that there was a substantially lower incidence of hemorrhage with the use of acenocoumarin than with other agents. This undoubtedly reflects the stability of hypoprothrombinemia which it was possible to achieve with this drug. In 3 of these cases, hemorrhage contributed to the death of the patients. Bishydroxycoumarin had been used in 2 of these cases, and acenocoumarin in 1 case, a hypertensive patient who died of cerebral hemorrhage.

TABLE IV. INCIDENCE OF HEMORRHAGE DURING THERAPY

ANTICOAGULANT	HEMORRHAGIC EPISODES	
	TOTAL NUMBER	AVERAGE NUMBER PER PATIENT PER YEAR OF THERAPY
Acenocoumarin	30	0.6
Bishydroxycoumarin	5	2.1
Ethyl biscoumacetate	4	2.9

On analyzing the site of bleeding in the patients with hemorrhage, it was observed that epistaxis occurred most frequently in hypertensive patients, that hematuria was associated most frequently with renal insufficiency, and that hemoptysis was noted particularly in patients with pulmonary embolism. Thus, many of these bleeding episodes are related to the basic disease process, and should not be attributed specifically to the use of anticoagulants. In particular, the presence of cardiorenal insufficiency in many patients has made it difficult to establish the proper dosage of anticoagulant, and has increased the likelihood

of hemorrhage. About half of the hemorrhagic episodes occurred in patients with cardiorenal failure.

The prothrombin level of patients at the time of hemorrhage is further evidence that factors other than anticoagulant therapy were involved in the onset of bleeding; prothrombin time averaged 20 per cent of normal when hemorrhage occurred in these patients. Conversely, extremely prolonged prothrombin times were observed in several instances without any evidence of hemorrhage, and the absence of hemorrhage under these circumstances was confirmed in 2 cases at autopsy.

Thromboembolic phenomena were encountered in 6 instances among the 382 patients studied. In only 2 patients was the prothrombin time within the therapeutic range at the time of the accident. On the other hand, there were 12 thromboembolic episodes occurring shortly after anticoagulant therapy was discontinued, 8 of which proved fatal.

There was a total of 29 deaths from all causes during anticoagulant therapy in the 382 patients. Autopsy was performed in 16 of these cases. There were 21 deaths among the 287 patients with coronary artery disease, only one of which could be related to the anticoagulant therapy. The other 8 deaths all occurred in patients with rheumatic valvular disease. Death was attributed to cardiac insufficiency in 14 patients, pulmonary or cerebral embolism in 3, hemorrhage in 2, shock in 2, and renal failure in 2. Three patients died of surgical diseases, and 3 patients died suddenly, probably on account of ventricular arrhythmia.

CONCLUSIONS

Of the three coumarin derivatives studied here, acenocoumarin is a more satisfactory agent than either bishydroxycoumarin or ethyl biscoumacetate for anticoagulant therapy, particularly in patients with coronary artery disease who require maintenance for long periods of time. While the effect of bishydroxycoumarin is sufficiently stable to be useful, its delayed action necessitates that heparin be used initially, and the persistence of hypoprothrombinemia after withdrawal increases the danger of hemorrhagic complications. Ethyl biscoumacetate, whose action is rapid and more easily subject to control, has produced in a number of cases marked fluctuations in prothrombin levels. The action of acenocoumarin, on the other hand, is intermediate in onset and duration, and prothrombin time is easily maintained within a therapeutic range.

The dosage of acenocoumarin employed in this study has been considerably lower than that recommended elsewhere.[1,4,5] The optimum loading dose in our patients proved to be 11 to 25 mg. over a period of 18 to 60 hours, and patients were thereafter maintained satisfactorily on an average of 3.6 mg. daily. This decreased dosage requirement may possibly be explained by differences in the selection of patients in the various studies. Our own patients, for the most part, suffered from coronary artery disease, while this was not the case in other published reports. We have ascertained that patients in cardiorenal failure require lower doses of anticoagulant than do other patients, and a substantial number of our cases were of this type. We have also observed that anticoagulant re-

quirements are reduced in patients whose prothrombin time is prolonged at the beginning of therapy.

In our experience with these anticoagulants, hemorrhagic and thromboembolic accidents have been infrequent. We have therefore considered the Quick method for determining prothrombin time, as performed in our laboratory under standard conditions, an adequate measure of the efficacy of anticoagulant therapy.

The mortality of patients with coronary artery disease appears to be markedly reduced with anticoagulant therapy. In the 382 cases reported here, most of which involved coronary artery disease, there were 29 deaths over a period of 650 treatment-months, a mortality of 7.6 per cent. This compares favorably with the mortality of untreated patients as reported recently by Nichol and his colleagues.[8]

SUMMARY

1. Anticoagulant therapy with coumarin derivatives has been employed in 382 patients, most of whom suffered from coronary artery disease.

2. Acenocoumarin (Sintrom) is preferred over the other coumarin derivatives studied because of the ease with which therapeutic levels of prothrombin could be maintained, as measured by the Quick prothrombin time test.

3. Doses of acenocoumarin required for satisfactory therapeutic control were considerably smaller than those usually recommended, particularly in patients with initially low levels of prothrombin and in patients with signs of cardiac or renal failure.

4. Hemorrhagic and thromboembolic accidents were infrequent in these patients, and it appears to us that the mortality of patients with coronary artery disease is markedly reduced by anticoagulant therapy.

Acenocoumarin (Sintrom) used in this study was kindly furnished by Geigy Pharmaceuticals, Division of Geigy (Canada) Limited, Montreal, Canada.

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Hemorrhagic Pericardial Effusion Following Myocardial Infarction Associated With a Ventricular Aneurysm

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Ventricular aneurysm accompanied by pericardial effusion occurs rarely as a complication of acute myocardial infarction. Schwartz[14] and Bean[3] each described a patient with myocardial infarction, ventricular aneurysm, and nonbloody pericardial effusion. Anderson and associates[1] reported a patient with hemopericardium and acute myocardial infarction in which an intact ventricular aneurysm was found at autopsy. The present paper describes a patient with recurrent hemorrhagic pericardial effusion occurring after an acute myocardial infarction, from whom a ventricular aneurysm was surgically removed with subsequent disappearance of the effusion.

CASE REPORT

E. D., a 50-year-old truck driver, had been in good health until Jan. 31, 1958, when he experienced the sudden onset of severe substernal chest pain which radiated to the jaw, down both arms, and was accompanied by profuse diaphoresis. He was hospitalized immediately. On admission his blood pressure was 80/60 mm. Hg, and an electrocardiogram showed evidence of an acute posterolateral myocardial infarction. The chest roentgenogram (Fig. 1) was normal. Four hours after admission his blood pressure rose to 110/80 mm. Hg, but he continued to have intermittent chest pain for 36 hours. Anticoagulation was accomplished with ethyl biscoumacetate, and the prothrombin levels were maintained between 28 and 35 per cent of control values during the entire hospitalization. A pericardial friction rub was never heard. His convalescence was uneventful until Mar. 1, when he developed mild anterior chest pain of pleuritic type and an associated elevation of temperature of 100°F., which persisted for 3 days. Chest roentgenogram at this time showed slight enlargement of the cardiac shadow. Anticoagulation was discontinued. Except for slight pleuritic pain on two occasions he remained asymptomatic and was discharged on Mar. 11. On April 1, he developed paroxysmal atrial tachycardia, which stopped following the administration of digitalis. Chest roentgenogram at this time showed a markedly enlarged cardiac shadow, and he was referred to the Durham Veterans Administration Hospital for further evaluation.

On admission to the Durham Veterans Administration Hospital, physical examination showed the blood pressure to be 110/90 mm. Hg, pulse 80, and respiration 18. There was a large congenital hemangioma on the right side of the face. The lungs were clear and the left border of cardiac dullness was 2 cm. to the left of the mid-clavicular line, with a well-localized point of maximal impulse 1 cm. medial to this. There was a Grade 3 apical systolic murmur. No rubs or gallops were heard. Abdominal examination revealed no abnormalities, and there was no peripheral edema. The antecubital venous pressure was 9 cm. of water, and the arm-to-tongue

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circulation time (Decholin) was 16 seconds. Laboratory data were as follows: Hb. 15 Gm. per cent; E.S.R. 18 mm. per hour (Wintrobe); WBC 6,800 per cubic millimeter; L.E. preparation negative; bleeding time (Duke) 3 minutes; clotting time (Lee-White) 10 minutes; prothrombin time 90 per cent of control; and B.U.N. 11 mg. per cent. Mantoux skin (1:100) tests on two occasions were negative. An electrocardiogram (Fig. 3) was consistent with a posterolateral myocardial infarction. The chest roentgenogram (Fig. 1) was interpreted as showing pericardial effusion.

The patient remained afebrile and experienced no further chest pain. On April 7, using the subxyphoid approach, a pericardiocentesis was performed and 50 c.c. of fluid was aspirated. The hematocrit reading of the fluid was 7 per cent, and it contained 1,666 WBC, with 98 per cent lymphocytes, and a protein content of 4.8 Gm. per 100 ml. Papanicolaou smears revealed no cells suggesting a malignancy. Cultures for *M. tuberculosis* on this and subsequent fluid were negative. The first pericardiocentesis was discontinued because of the occurrence of syncope; however, on the following day 450 c.c. of similar fluid was aspirated and 150 c.c. of air instilled into the pericardium. Fluoroscopy demonstrated a mass on the lateral wall of the heart (Fig. 1).

The patient was managed conservatively and was asymptomatic when discharged from the hospital. He returned on May 4, complaining of right upper quadrant pain. At this time the blood pressure determinations revealed 15 mm. Hg of paradoxical pulse. There was obvious distention of the neck veins, and the liver was palpable 4 cm. below the right costal margin. On May 5, another pericardiocentesis was performed and 745 c.c. of fluid with a hematocrit of 4.5 per cent was withdrawn. Following this procedure the signs of cardiac tamponade disappeared. The fluid reaccumulated very rapidly, and surgical exploration was planned. On May 21, 1,500 c.c. of fluid (hematocrit 2.5 per cent) was aspirated, in preparation for operation.

On May 23, a left thoracotomy was performed. The pericardium was opened and about 1,500 c.c. of bloody fluid was removed. A large aneurysm of the left ventricle was found along the posterior lateral aspect. The superior edge was about 2 cm. below the left circumflex coronary artery, and the anterior edge was about 3 to 4 cm. from the left anterior descending coronary artery. Paradoxical pulsation was prominent. A large DeBakey clamp was placed across the base of the aneurysm from the inferior margin. A second clamp, applied from the superior margin, was necessary to obtain complete compression. Interrupted mattress sutures were placed just distal to the DeBakey clamp. Ivalon pledgets were placed under the loops of suture to prevent tearing of the myocardium. A longitudinal incision was made in the apex of the aneurysm for a distance of about 6 cm. The wall of the aneurysm was found to be about 2 mm. in thickness, and an underlying thrombus filled the aneurysmal sac distal to the clamp. The thrombus was removed and the clamps were momentarily released, allowing blood to wash out smaller bits of thrombus. After reapplication of the clamps the mattress sutures were tied down over the Ivalon pledgets. The excess portion of the aneurysm was excised, leaving a 2-cm. cuff protruding from the epicardial surface of the heart (Fig. 4). An 8 by 10-cm. window of pericardium was removed anteriorly. No closure of the large redundant pericardial sac was attempted.

Microscopic sections of the wall of the aneurysm revealed that the myocardium was almost entirely replaced by fibrous tissue. The pericardium showed chronic pericarditis (Fig. 2).

The patient made an uneventful recovery from the operation and was discharged on June 8. He returned for an outpatient visit on August 6, and was doing well. His blood pressure was 140/70 mm. Hg, and the chest roentgenogram showed bulging of the left heart border, but there was no reaccumulation of fluid. The Grade 3 apical systolic murmur was still audible.

On Sept. 16, the patient returned, complaining of palpitations. The chest roentgenogram revealed a marked localized enlargement of the cardiac shadow, which was felt to be a recurrent aneurysm. An attempt was made to repair the aneurysm, using extracorporeal circulation. However, when the clamp was applied across the aneurysm, the patient developed ventricular fibrillation and expired.

Autopsy.—At autopsy, the heart weighed 375 grams. There was a 6 by 5-cm. false aneurysm near the old suture line which communicated with the ventricular cavity. The wall was 1 mm. thick. A firm thrombus, measuring 3 by 3 cm., was found in the residual aneurysmal sac. This thrombus was behind the lateral leaflet of the mitral valve and held the valve in extension, thus preventing adequate closure.

Fig. 1.—*A*, PA chest film taken the day myocardial infarction occurred. *B*, PA chest film 6 wk. after the infarction, showing a slight localized bulge along the left heart border. *C*, PA chest film 2 mo. after the infarction, showing a marked increase in the cardiac shadow. *D*, PA chest film 3½ mo. after the infarction, with the patient tilted to the right. A protrusion of the left heart border was demonstrated by removing 450 c.c. of fluid and injecting 150 c.c. of air into the pericardial sac. *E*, PA chest film 4½ mo. after the infarction, showing reaccumulation of pericardial fluid after pericardiocentesis 1 mo. prior. Signs and symptoms of pericardial tamponade were present. *F*, PA chest film 10 days after aneurysmorrhaphy, showing decrease in the cardiac silhouette, with a distinct bulge on the left heart border caused by the large protruding cuff of aneurysm which was left attached.

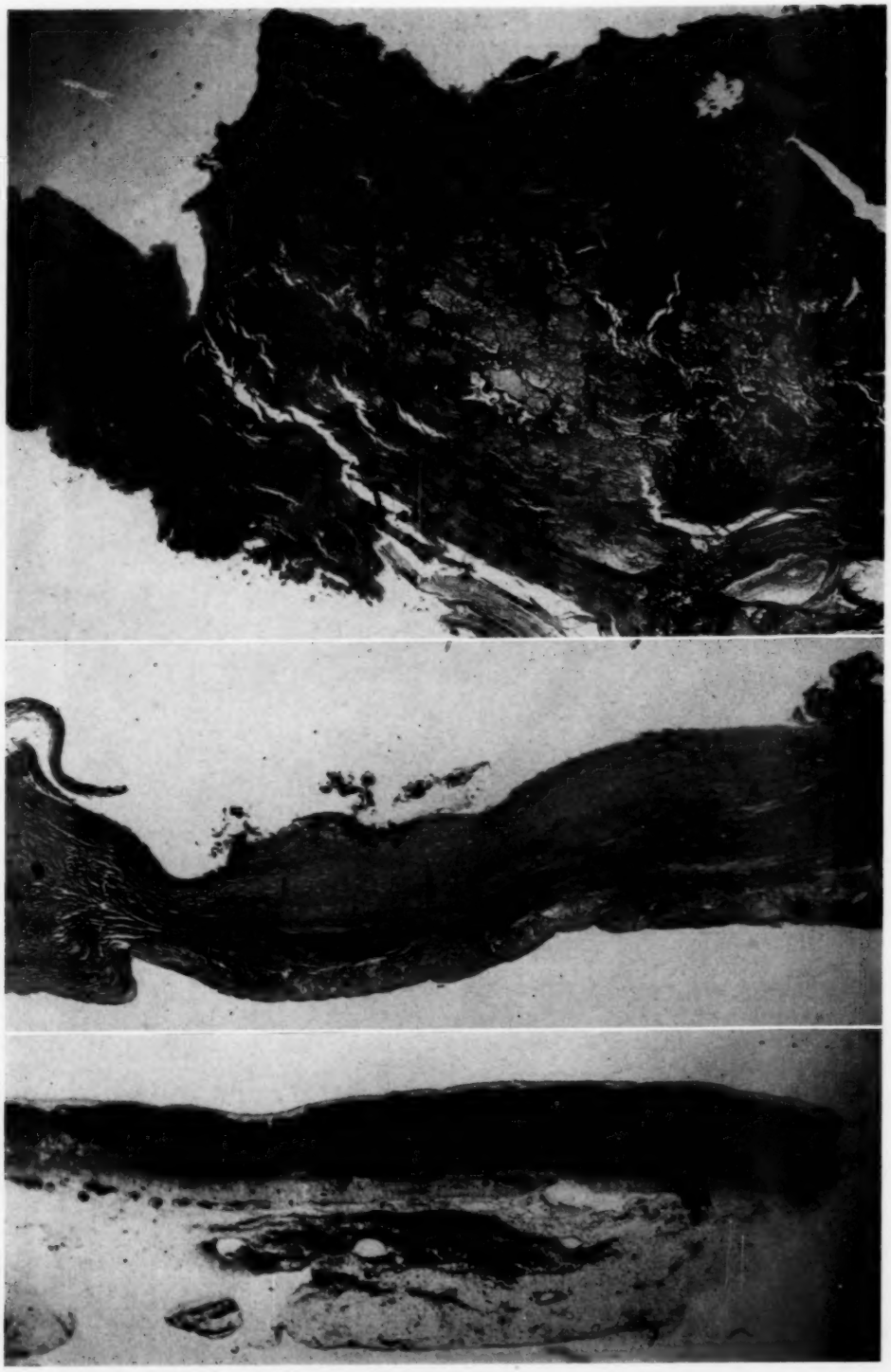

Fig. 2.—Photomicrographs (× 15; reduced 2/9) of the surgical specimens with inner surfaces toward the top of the page. *A*, A portion of the thrombus which filled the apex of the aneurysm. *B*, The thin, scarred apical portion of the aneurysm. *C*, The organizing hemorrhage beneath a mesothelial surface. There is some recent hemorrhage in the pericardial fat which is probably operative.

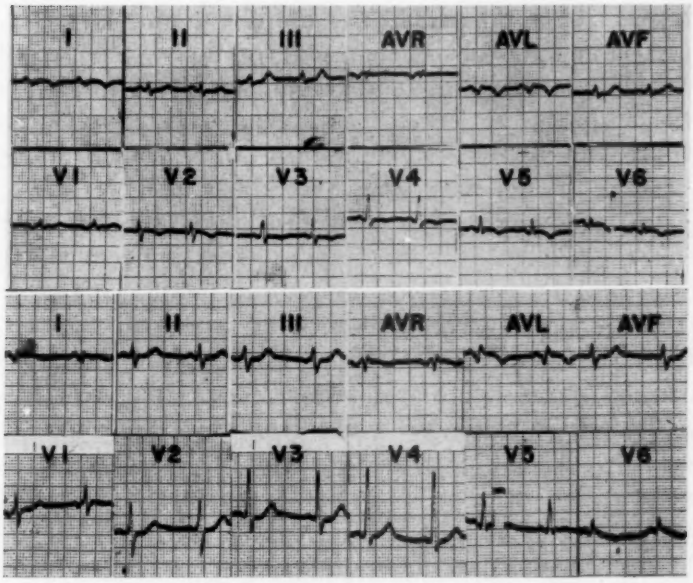

Fig. 3.—*A*, ECG of April 2, 1958, shows posterolateral myocardial infarction, with persistent S-T and T-wave changes. Negative T waves over the precordium and low amplitude are consistent with pericardial effusion. *B*, Postoperative ECG of June 7, 1958, shows slight increase in conduction time (0.10 to 0.11 sec.), positive precordial T waves, and increased amplitude.

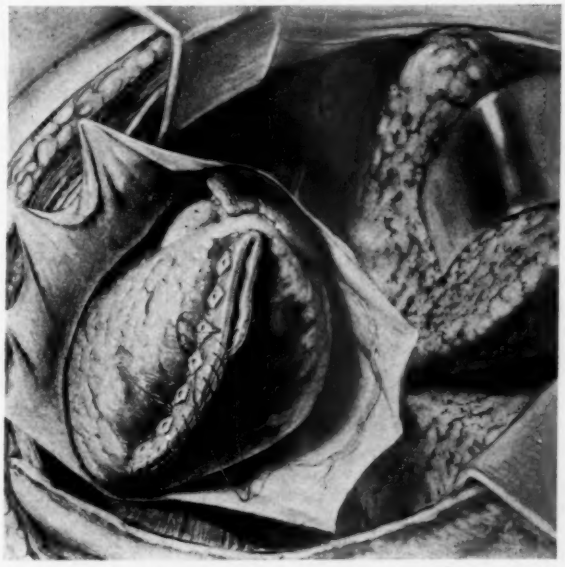

Fig. 4.—Drawing of the heart after aneurysmorrhaphy, showing the redundant pericardial sac and the protruding cuff of the aneurysmal sac.

DISCUSSION

The progressively downhill course experienced by patients with ventricular aneurysm has been emphasized by Schlichter and associates.[13] Excision of ventricular aneurysms has been advocated by Bailey and associates[2] and by

Cooley and associates[4] to prevent heart failure and embolism. In this case the procedure had also apparently stopped the formation of bloody pericardial fluid.

Two possible explanations exist to account for the formation of hemorrhagic pericardial effusion in this patient. First, the aneurysm may actually have been leaking. However, no evidence was found for this at the time of operation or on microscopic sections of the aneurysm. Second, and more likely, is the possibility that hemorrhagic pericarditis developed and was mechanically aggravated by the aneurysm. It seemed likely that the aneurysm played some role in the formation of the fluid, since effusion ceased abruptly following surgery. Dressler[5] recently described a "postmyocardial infarction" syndrome which is characterized by recurrent fever, pneumonitis, pleuropericardial pain, and pleural and pericardial effusions. According to this author, hemorrhagic pericarditis may be the only manifestation. Dressler[6] considered this syndrome to be a hypersensitivity reaction. The clinical course of our patient differed from that of the reported cases of postmyocardial infarction hemorrhagic pericarditis in that the effusion was not self-limited but recurred rapidly.[6,10,15] Also, he had only a 3-day episode of fever and chest pain occurring during the convalescent period, which was much shorter than in the other reported cases.

Several patients with hemorrhagic pericardial effusion who had received anticoagulant therapy following myocardial infarction have been reported.[7-9,11,12] In most of these patients the prothrombin time was below therapeutic range at the time the effusion developed; however, hemorrhagic pericardial effusion has been reported complicating myocardial infarction in the absence of anticoagulant therapy.[1] In this case the prothrombin determinations were never below 25 per cent of the control. The major effusion occurred after anticoagulation was discontinued, at which time the prothrombin concentrations were normal. Thus, it seems unlikely that anticoagulant therapy was the causative agent.

SUMMARY

Recurrent hemorrhagic pericardial effusion associated with a ventricular aneurysm occurs rarely as a complication of acute myocardial infarction. This paper describes a patient in which an intact ventricular aneurysm was surgically removed and the formation of effusion stopped.

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Etiological Factors Concerned With the Causation of Heart Disease in Turkey

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It is known that with the introduction of antibiotics to medicine, the ratio of deaths caused by infectious diseases was greatly reduced. Undoubtedly, better hygienic conditions have been a very important factor in this reduction. Malaria, once one of the greatest disabling illnesses in Turkey, is now among the rare diseases, and cholera, plague, and smallpox are subjects read about only in books. In surgery the mortality rate has been greatly decreased by means of modern anesthesiology, blood transfusions, anticoagulants, etc. Improvements in living conditions, as well as various other reasons, have caused the mortality rate to decrease. However, lesions of the cardiovascular system and malignant illnesses have assumed first place among the causes of death. In the Medical Clinics of Ankara, Gülhane Military Academy of Medicine, during the year 1951-1952, the infectious diseases ranked first among the causes of death, with an incidence of 37.5 per cent, and lesions of the cardiovascular system ranked third, with an incidence of 15 per cent. In the year 1957-1958, heart diseases have taken first place, with an incidence of 38.6 per cent, while malignant diseases are in second place, with an incidence of 27.3 per cent. During this same period, the infectious diseases have been relegated to last place, with an incidence of 6.8 per cent.

It is extremely important to determine the causes of cardiac diseases for reasons of (1) prognosis, (2) prophylaxis, and (3) treatment. Since this subject has not been considered adequately in Turkey, we began to study the etiology of heart diseases in our country in order to determine the frequency of various types of cardiac diseases here, and also to decide what means of prevention can be employed.

METHOD AND CASES

We took as our guide for etiological diagnosis the New York Heart Association's *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels*.[1] We have followed this small but very valuable international book quite strictly, with particular attention to diagnosis and

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classification. We employ this book in both our clinical and private practice for diagnosis and classification of the disease. Whenever we were uncertain regarding any problem, we consulted authorities in the United States by private communication and were always welcomed with great interest.

In some statistics, only the organic heart diseases have been taken into consideration, but as stated in the aforementioned book, "Diseases of the heart include not only the structural changes found in the heart, pericardium, and adjacent arterial structure but also such disturbances of the functions of the heart as are manifested by arrhythmia, by its ability to perform its function as a pump and by its tendency to give rise to abnormal sensations." Therefore, the so-called functional disturbances of the heart are also included in our study.

Our cases have been taken from the archives of the Medical Service, Gülhane Army Medical Center, and from the office archives of the senior author. Although the Gülhane Hospital is a military hospital, more than 50 per cent of its patients are civilians, because it is a teaching hospital.

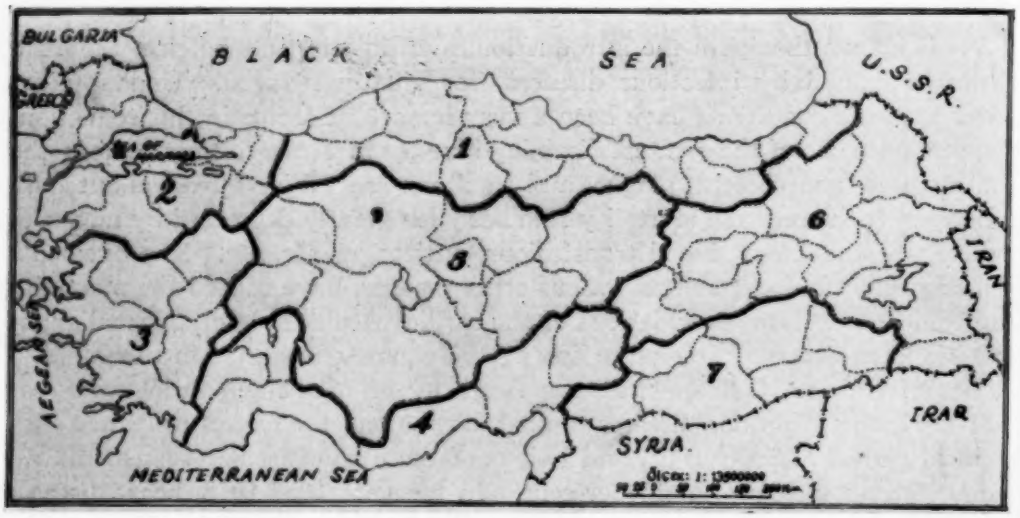

Fig. 1.—Geographic divisions of Turkey. *1*, **Black Sea Region.** *2*, **Sea of Marmara Region.** *3*, **Aegean Sea Region.** *4*, **Mediterranean Region.** *5*, **Central Anatolia Region.** *6*, **Eastern Anatolia Region.** *7*, **Southeastern Anatolia Region.**

As is well known, Turkey is a bridge between Europe and Asia. Its area is 776,970 square kilometers and consists of 67 provinces (vilâyet). Its population is 24,111,778, according to the 1955 census. Geographically, it is divided into 7 regions: (1) Black Sea Region: The climate of this area is mild and there is much rainfall. Away from the coastline, toward the inner parts of the land, the climate becomes more severe. (2) Sea of Marmara Region: In this area the summers are hot and sunny and the winters are not very cold. (3) Aegean Sea Region: Here the summers are rather hot and rainless but the winters are mild and rainy. (4) Mediterranean Region: In this region the summers are hot and rainless and the winters are mild and rainy. (5) Central Anatolia Region: This area is surrounded by high mountains and is closed to sea currents. The winters are very cold and the summers are hot and dry. Rain falls very often in spring and there is snow in winter. (6) Eastern Anatolia Region: This region is the coldest part of Turkey because it is very high. The winters are very cold and long, and yet there is no moisture. The summers are short and not very hot. (7) Southeastern Anatolia Region: The summers here are very long and rather hot and the winters are cold. (See Fig. 1.)

Ankara is the heart of Turkey. However, most of the patients included in our statistics are people who developed illnesses while living in provinces other than Ankara, and who have come to Ankara for cardiac consultation. Only 5.8 per cent of the patients were born and grew up in Ankara. Although our number of cases is small, there are representative cases from all the provinces and villages of Turkey, so that our material is not limited to Ankara.

The patients in whom no cardiac disease was discovered but whose course should be followed by periodic examinations because of the presence or history of an etiological factor which might cause heart disease (no heart disease: predisposing etiological factor) and undiagnosed manifestations are not included in our study. The patients included in the groups termed "Reflex Disturbances of the Heart" and "Neurocirculatory Asthenia" had signs and symptoms for at least six months. The ordinary neuroses and temporary premature beats are not included in this study.

RESULTS

The records of 3,245 patients who were affected with heart trouble, and who came from 67 different provinces of Turkey, were studied meticulously. Of these, 1,760 (54 per cent) were taken from hospital archives and 1,485 (46 per

TABLE I. ETIOLOGICAL FACTORS OF HEART DISEASES IN DESCENDING ORDER OF FREQUENCY

ETIOLOGICAL FACTORS	TOTAL		MALE		FEMALE	
	NUMBER OF CASES	PER CENT	NUMBER OF CASES	PER CENT	NUMBER OF CASES	PER CENT
Rheumatic fever	888	27.3	540	26.7	348	28.4
Arteriosclerosis	842	25.9	663	32.9	179	14.6
Systemic hypertension	658	20.3	272	13.5	386	31.4
Neurocirculatory asthenia	354	10.9	200	9.9	154	12.5
Reflex disturbances of the heart	140	4.3	87	4.3	53	4.3
Pulmonary hypertension	121	3.7	93	4.6	28	2.3
Anemia	54	1.6	37	1.8	17	1.4
Bacterial infection	51	1.6	35	1.7	16	1.3
Unknown	51	1.6	39	1.9	12	1.0
Congenital anomaly	42	1.3	33	1.6	9	0.7
Hyperthyroidism	22	0.7	5	0.3	17	1.4
Syphilis	12	0.4	10	0.5	2	0.2
Hypothyroidism	6	0.2	1	0.1	5	0.4
Toxic agents	2	0.1	1	0.1	1	0.1
Parasitic illnesses	2	0.1	2	0.1	0	0.0
Total	3,245	100.0	2,018	100.0	1,227	100.0

TABLE II. THE DISTRIBUTION OF CASES ACCORDING TO THE SEVEN REGIONS OF TURKEY

REGION	TOTAL		MALE		FEMALE	
	NUMBER OF CASES	PER CENT	NUMBER OF CASES	PER CENT	NUMBER OF CASES	PER CENT
Black Sea Region	577	17.8	359	17.8	218	17.8
Sea of Marmara Region	746	23.0	464	23.0	282	23.0
Aegean Sea Region	232	7.1	146	7.2	86	7.0
Mediterranean Region	193	5.9	129	6.4	64	5.2
Central Anatolia Region	1,021	31.5	605	30.0	416	33.9
Eastern Anatolia Region	315	9.7	209	10.4	106	8.6
Southeastern Anatolia Region	161	5.0	106	5.2	55	4.5
Total	3,245	100.0	2,018	100.0	1,227	100.0

cent) from the archives of private practice. There were 1,227 (38 per cent) females and 2,018 (62 per cent) males. The age of these patients varied between 3 and 86 years.

As seen from Table I, rheumatic fever is the leading cause of heart disease, with an incidence of 27.3 per cent. Next is arteriosclerosis, with an incidence of 25.9 per cent, and arterial hypertension, with an incidence of 20.3 per cent. These three diseases account for 73.5 per cent of all cases studied. These three entities are also the main etiological factors in heart disease in other parts of the world. We have noticed that arteriosclerosis is the leading cause of heart disease in the United States, while rheumatic fever is first in Turkey. Both in hospital and private practice the cardiac diseases according to etiology were the same.

The following percentages are obtained if the cases are grouped according to sex. In males, arteriosclerosis assumes first place, with an incidence of 32.9 per cent. In females, hypertension takes first place, with an incidence of 31.4 per cent (Table I).

When we study Table II, we find the following geographical distribution: 31.5 per cent from Central Anatolia; 23 per cent from the Sea of Marmara; 17.8 per cent from the Black Sea; 9.7 per cent from Eastern Anatolia; 7.1 per cent from the Aegean Sea; 5.9 per cent from the Mediterranean; and 5 per cent were from Southeastern Anatolia.

Table III shows us the causes of illness and divides the cases according to the patients' age groups. When we study this table, we note that during the first decade, rheumatic heart disease and congenital abnormalities are most prevalent. More than 50 per cent of these cases are rheumatic heart disease. In this age group the incidence of acute rheumatic fever is very high. In some people who have recovered from rheumatic fever we can find the signs of cardiac disease immediately, but in others, carditis is insidious in onset and the signs of disease appear at an older age. For this reason the incidence of rheumatic heart disease between the ages of 11 and 20 years is increasing, and reaches a maximum between the ages of 21 and 30 years. In many such patients, heart failure and death occur after these ages. After the age of 40 the incidence of rheumatic heart diseases is decreasing and that of arteriosclerosis is increasing. Eighty-one per cent of all cases give a history of having had polyarthralgia. Of these, typical polyarthritis has been noted in 67 per cent, and atypical arthralgic complaints have been noted in 14 per cent. On the coastline of the Black Sea and in the region of the Sea of Marmara, as among the people of Central Anatolia, rheumatic heart diseases were the most common of the cardiac diseases encountered. In these regions, rheumatic fever is the leading cause of heart trouble.

Arteriosclerotic heart disease appears between the ages of 21 and 30, and reaches a maximum between the ages of 51 and 60. After the age of 60, the incidence gradually decreases. There are very few cases of arteriosclerotic heart disease among women younger than 40. After the age of 50, sexual differences diminish. The following series shows the percentage of arteriosclerotic heart disease in patients from the various regions of Turkey, in comparison to other kinds of cardiac conditions in each region: (1) Southeastern Anatolia Region, 36.0 per cent, (2) Eastern Anatolia Region, 33.6 per cent, (3) Marmara

TABLE III. ETIOLOGICAL FACTORS AND NUMBER OF CASES ACCORDING TO AGE AND SEX

ETIOLOGICAL FACTORS	TOTAL CASES	NUMBER OF CASES ACCORDING TO AGE (BY DECADE)								
		1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90
Total	3,245	21	211	656	484	659	812	324	72	6
Rheumatic fever	888	12	165	384	136	103	63	22	3	0
Arteriosclerosis	842	0	0	4	50	244	376	139	25	4
Systemic hypertension	658	0	8	25	71	174	254	98	27	1
Neurocirculatory asthenia	354	0	11	130	144	52	15	2	0	0
Reflex disturbances of the heart	140	0	4	44	41	26	16	7	2	0
Pulmonary hypertension	121	0	1	0	3	22	52	37	6	0
Anemia	54	0	8	18	15	6	4	1	2	0
Bacterial infection	51	1	6	25	9	8	2	0	0	0
Unknown	51	0	0	2	4	8	18	13	5	1
Congenital anomaly	42	8	7	17	5	3	1	0	1	0
Hyperthyroidism	22	0	1	6	3	4	5	2	1	0
Syphilis	12	0	0	0	0	5	4	3	0	0
Hypothyroidism	6	0	0	0	1	4	1	0	0	0
Toxic agents	2	0	0	0	1	0	1	0	0	0
Parasitic illnesses	2	0	0	1	1	0	0	0	0	0
Male										
Total	2,018	11	139	434	266	405	519	194	46	4
Arteriosclerosis	663	0	0	4	48	203	285	102	18	3
Rheumatic fever	540	6	113	277	51	40	35	15	3	0
Systemic hypertension	272	0	3	13	30	69	110	35	11	1
Neurocirculatory asthenia	200	0	3	60	87	36	13	1	0	0
Pulmonary hypertension	93	0	0	0	3	17	44	24	5	0
Reflex disturbances of the heart	87	0	2	24	26	19	9	6	1	0
Unknown	39	0	0	2	3	7	14	8	5	0
Anemia	37	0	6	12	8	4	4	1	2	0
Bacterial infection	35	0	5	22	5	2	1	0	0	0
Congenital anomaly	33	5	7	15	2	2	1	0	1	0
Syphilis	10	0	0	0	0	5	3	2	0	0
Hyperthyroidism	5	0	0	4	1	0	0	0	0	0
Parasitic illnesses	2	0	0	1	1	0	0	0	0	0
Hypothyroidism	1	0	0	0	0	1	0	0	0	0
Toxic agents	1	0	0	0	1	0	0	0	0	0
Female										
Total	1,227	10	72	222	218	254	293	130	26	2
Systemic hypertension	386	0	5	12	41	105	144	63	16	0
Rheumatic fever	348	6	52	107	85	63	28	7	0	0
Arteriosclerosis	179	0	0	0	2	41	91	37	7	1
Neurocirculatory asthenia	154	0	8	70	57	16	2	1	0	0
Reflex disturbances of the heart	53	0	2	20	15	7	7	1	1	0
Pulmonary hypertension	28	0	1	0	0	5	8	13	1	0
Anemia	17	0	2	6	7	2	0	0	0	0
Hyperthyroidism	17	0	1	2	2	4	5	2	1	0
Bacterial infection	16	1	1	3	4	6	1	0	0	0
Unknown	12	0	0	0	1	1	4	5	0	1
Congenital anomaly	9	3	0	2	3	1	0	0	0	0
Hypothyroidism	5	0	0	0	1	3	1	0	0	0
Syphilis	2	0	0	0	0	0	1	1	0	0
Toxic agents	1	0	0	0	0	0	1	0	0	0
Parasitic illnesses	0	0	0	0	0	0	0	0	0	0

TABLE IV. ETIOLOGICAL FACTORS AND NUMBER OF CASES ACCORDING TO REGIONS

ETIOLOGICAL FACTORS	TOTAL	BLACK SEA	SEA OF MARMARA	AEGEAN SEA	MEDITERRANEAN	CENTRAL ANATOLIA	EASTERN ANATOLIA	SOUTHEASTERN ANATOLIA
Total	3,245	577	746	232	193	1,021	315	161
Rheumatic fever	888	189	134	68	56	325	77	39
Arteriosclerosis	842	101	239	54	37	247	106	58
Systemic hypertension	658	137	185	34	31	201	40	30
Neurocirculatory asthenia	354	69	101	21	19	94	38	12
Reflex disturbances of the heart	140	13	37	16	21	35	15	3
Pulmonary hypertension	121	18	16	12	11	39	20	5
Anemia	54	15	4	7	3	18	3	4
Bacterial infection	51	12	8	7	5	11	5	3
Unknown	51	6	5	7	4	26	2	1
Congenital anomaly	42	7	9	6	3	11	4	2
Hyperthyroidism	22	7	4	0	1	7	3	0
Syphilis	12	1	3	0	2	3	0	3
Hypothyroidism	6	1	0	0	0	3	1	1
Toxic agents	2	1	0	0	0	1	0	0
Parasitic illnesses	2	0	1	0	0	0	1	0
Male								
Total	2,018	359	464	146	129	605	209	106
Arteriosclerosis	663	72	191	42	29	198	86	45
Rheumatic fever	540	134	76	45	39	175	43	28
Systemic hypertension	272	64	75	14	15	77	15	12
Neurocirculatory asthenia	200	34	63	10	11	49	28	5
Pulmonary hypertension	93	14	13	7	8	31	16	4
Reflex disturbances of the heart	87	8	23	9	12	22	11	2
Unknown	39	3	3	4	4	23	1	1
Anemia	37	12	4	4	3	10	1	3
Bacterial infection	35	10	6	6	3	5	3	2
Congenital anomaly	33	5	6	5	3	9	3	2
Syphilis	10	1	3	0	2	2	0	2
Hyperthyroidism	5	2	0	0	0	2	1	0
Parasitic illnesses	2	0	1	0	0	0	1	0
Hypothyroidism	1	0	0	0	0	1	0	0
Toxic agents	1	0	0	0	0	1	0	0
Female								
Total	1,227	218	282	86	64	416	106	55
Systemic hypertension	386	73	110	20	16	124	25	18
Rheumatic fever	348	55	58	23	17	150	34	11
Arteriosclerosis	179	29	48	12	8	49	20	13
Neurocirculatory asthenia	154	35	38	11	8	45	10	7
Reflex disturbances of the heart	53	5	14	7	9	13	4	1
Pulmonary hypertension	28	4	3	5	3	8	4	1
Anemia	17	3	0	3	0	8	2	1
Hyperthyroidism	17	5	4	0	1	5	2	0
Bacterial infection	16	2	2	1	2	6	2	1
Unknown	12	3	2	3	0	3	1	0
Congenital anomaly	9	2	3	1	0	2	1	0
Hypothyroidism	5	1	0	0	0	2	1	1
Syphilis	2	0	0	0	0	1	0	1
Toxic agents	1	1	0	0	0	0	0	0
Parasitic illnesses	0	0	0	0	0	0	0	0

Sea Region, 32.0 per cent, (4) Central Anatolia Region, 24.1 per cent, (5) Aegean Sea Region, 23.3 per cent, (6) Mediterranean Region, 19.1 per cent, (7) Black Sea Region, 17.5 per cent.

By studying the preceding figures we can see that arteriosclerotic heart disease is particularly common in Southeastern Anatolia. This is very interesting because in the provinces of Diyarbakir, Urfa, Adiyaman, Gaziantep, Mardin, and Siirt the people consume a great deal of butter and other animal fats. Although exact figures are not obtainable, we were able to approximate the amount consumed by asking our patients how much butter they used in a month's time or what kinds of food they ate at breakfast, dinner, and supper. Our conclusion is that each person in these provinces consumes at least 100 grams of butter fat, and that those from wealthier families, who form the majority of our cases, have at least 150 to 250 grams of animal fat daily. The people of the Black Sea Region live mostly on corn and fish. Considering these two facts, we judge that butter and animal fats may be important factors in the etiology of arteriosclerotic heart diseases, and that corn oil has an antiarteriosclerotic effect.

Hypertensive heart diseases begin in a younger age group than does arteriosclerotic diseases. The cause of this is the high prevalence of diffuse glomerulonephritis in the younger age groups of Turkey. Arterial hypertension is the main cause of heart diseases in the female population of Turkey. Geographically, although cases of hypertension are seen predominantly in the Marmara Sea and Black Sea Regions, the incidence of hypertensive heart disease has slight variation over all of Turkey. (See Table IV.)

The congenital heart diseases form 1.29 per cent, and neurocirculatory asthenia forms 10 per cent, of all heart diseases in Turkey. The cardiac conditions secondary to pulmonary hypertension (cor pulmonale) form 3.72 per cent of all the cases. Syphilitic heart diseases are so rare (0.4 per cent) that there is no need to consider them.

SUMMARY

Of the causes of heart diseases among 3,245 cases studied, from all provinces of Turkey, rheumatic fever, arteriosclerosis, and hypertension constitute 73.5 per cent. In females the leading cause is hypertension, and in males it is arteriosclerosis. Rheumatic heart diseases are seen in the younger age groups and arteriosclerotic and hypertensive heart diseases are seen in the older age groups. In Southeastern Anatolia, we encounter arteriosclerosis most commonly, and in Central Anatolia and the Black Sea Region we find rheumatic fever to be most prevalent.

The incidence of heart diseases due to anemia, infections, and congenital defects is approximately 1.5 per cent each. The incidence of hyperthyroidism, toxic agents, syphilis, and parasitic illnesses is less than 1 per cent each.

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A New Vectorcardiographic Lead System

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Some of the many vectorcardiographic lead systems which have been described during the last 2 decades[8] have special advantages, in that the error of proximity potentials or of excentricity of the heart is kept small in some of the systems. On the other hand, it is probably a disadvantage in most of these methods that their coordinate system does correspond to the coordinate system of the body, but not to that of the normal heart. In other words, the sagittal plane of most of the currently used vectorcardiographic lead systems corresponds to a vertical axis, and the transversal plane corresponds to a horizontal axis. Actually, the longitudinal axis of the heart in most cases is not vertical, but includes an angle of about 60 degrees with the horizontal line. In cases of left ventricular hypertrophy this angle becomes smaller.

Already in 1934, Trendelenburg[6] recommended electrocardiographic leads (by putting the left leg electrode on the left side of the chest) which would better correspond to the longitudinal axis of the heart. In regard to vectorcardiography, Milnor[3] mentioned the lack of correspondence between the standard planes of usual vectorcardiographic systems and the planes which usually are included by the QRS loops.

We are, therefore, describing here a vectorcardiographic lead system the planes of which correspond better to the planes of symmetry of the heart. Six electrodes are used. Two of them are put on each upper arm, so that the centers of the shoulder articulations may be regarded as actual corner points of the coordinate system. The distance between both shoulders is measured and an equal distance is measured on both lateral sides of the chest. On the resulting points two other electrodes are situated. In this way a quadrate is formed. The crossing points of its diagonals on the chest walls correspond to the anterior and posterior electrode placements on the chest. Fig. 1 shows the electrode placements.

The sagittal plane of our lead system is inclined from the right shoulder to the left chest wall and includes an angle of 45 degrees with the horizontal line.

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It, therefore, corresponds rather closely to the plane of the atrial and ventricular septums of the normal heart. Hearts with slight left ventricular hypertrophy whose longitudinal axis is deviated a little more toward the left than that of normal hearts correspond still better with the coordinates of our system, because their sagittal plane may include an angle of about 45 degrees with the horizontal line. The transversal plane of this electrode system is declined from the left shoulder to the right lateral chest wall. It again corresponds better to the actual transversal plane of a normal heart or of a heart with slight left ventricular hypertrophy. We, therefore, believe that we are better able to anticipate the conditions present in hypertrophy of the ventricles, as shown vectorcardiographically in the lead system described in this paper, since the relative vector loops are registered in a plane which corresponds most closely to the actual transversal plane of most hearts and not to its projection on the horizontal plane.

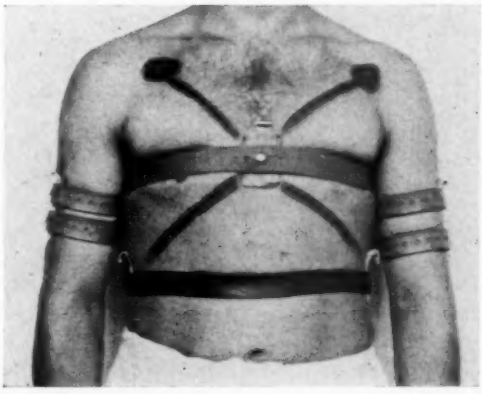


Fig. 1.—The photograph shows the electrode placements. Two of the broad electrodes are placed on the upper arms and two on those points of the lateral chest wall which have the same distance from the center of the respective shoulder as is the distance between both shoulders. In this way a quadrate is formed. The crossing points of its diagonals as marked on the anterior and posterior chest walls correspond to the fifth and sixth electrode positions.

Further advantages of this lead system are offered by the possibility of using broad electrodes, which are better in preventing artificial changes of the loops. The use of two arm electrodes offers the possibility of having two absolutely fixed electrodes. Also, the other electrodes are easily placed accurately. Hence, we can state that the reproducibility of vector loops at different times, registered by different workers on the same patient, is good. Finally, as already mentioned above, we think that the transversal plane is more sensible to changes of the ventricular musculature, especially in cases of ventricular hypertrophy, and less sensible to positional changes of the heart, compared to the horizontal plane used in most other lead systems as representative of the transversal plane.

The normal vector loops as recorded by this method differ in certain respects from the vector loops registered by other methods. By the fact that the longitudinal axis of our system is not vertical, but oblique from the right superiorly toward the left inferiorly, the vector loops in the frontal plane differ in 45 degrees from the usual frontal vectorcardiograms. Normal frontal QRS vector loops as

shown in Fig. 2 (36-year-old doctor in good health) are directed inferiorly and a little toward the right. An electrical axis of QRS of 60 degrees as registered in the usual vector lead systems corresponds to an angle of 105 degrees in our system. Normal frontal QRS loops are mostly narrow and show a positive sense of rotation. Sometimes we also observed figure-of-eight loops, very rarely

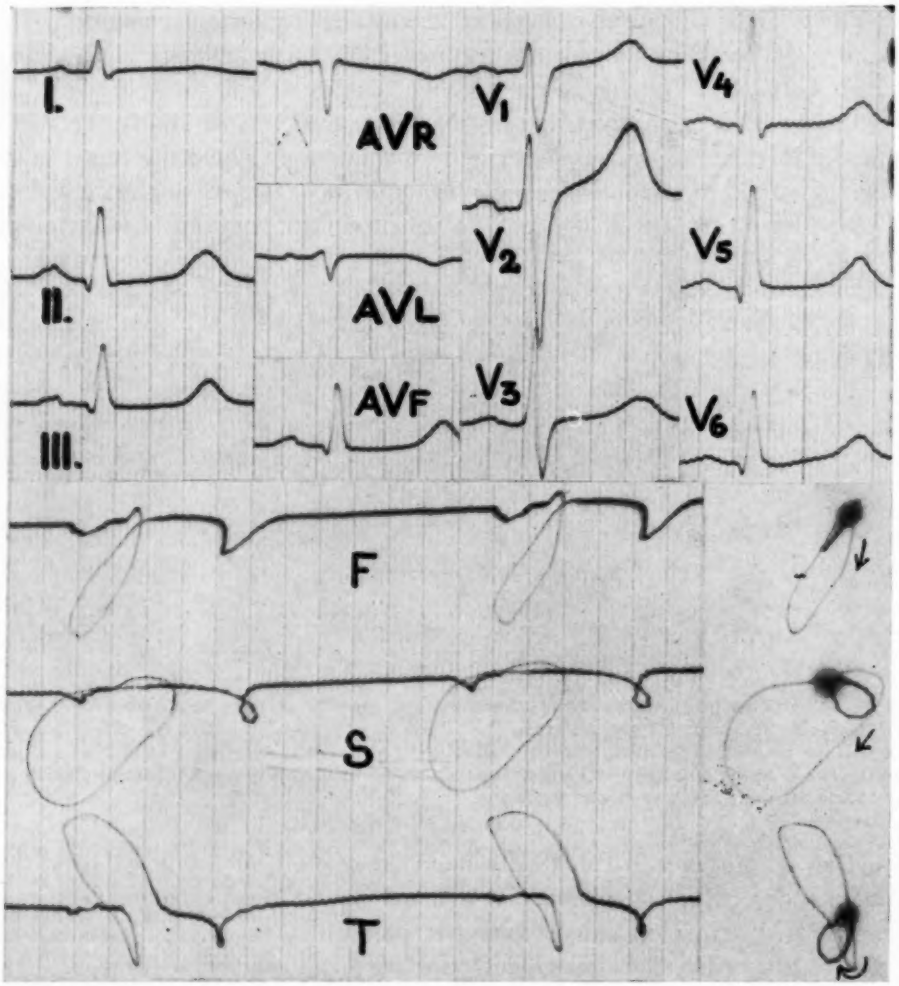


Fig. 2.—Electro- and vectorcardiograms of a normal person (36 years old). The frontal QRS vector loops are directed inferiorly and to the right and show a clockwise rotation. The sagittal QRS loops are wide, directed anteriorly initially, and inferiorly and posteriorly later on, and show likewise a clockwise rotation. The P and T vector loops are included in the QRS loops. The transversal QRS loop is narrow, directed anteriorly in the beginning and posteriorly later on. It likewise shows a clockwise rotation. The T loops are parallel to the first part of the QRS.

a negative sense of rotation. P and T vector loops are included in, or are parallel to, the QRS vector loops. The sagittal QRS vector loop is usually wider than that of other systems. The reason for this is that our sagittal plane corresponds better to the sagittal plane of symmetry of the heart; therefore, the potentials developed in this direction are registered optimally and with greater amplitude

than by other lead systems, which use vertical sagittal planes. With other systems only a projection on the vertical plane, which shows smaller amplitudes of loops, may be registered. Also, in the sagittal plane, P and T vector loops usually are included in the QRS vector loops.

In our opinion, the transversal QRS vector loops correspond better to the actual development of bioelectric potential in the transversal plane of the heart than do loops registered in a horizontal plane. They are rather narrow in most cases and show almost always a positive (clockwise) sense of rotation. Their first part is directed anteriorly, and their second part is directed posteriorly. Normally, the P and T vector loops are in most cases parallel to the first part of the QRS vector loops.

P vector loops are shown well by the method of registration described in this paper, as shown previously.[2] In cases with pulmonary P waves the P vector loops are long and have a counterclockwise rotation. In cases with mitral P waves the P vector loops are irregular and develop especially toward the left and posteriorly. In cases of slight or moderate left ventricular hypertrophy the QRS vector loop is tilted toward the left superiorly along a longitudinal axis. A positive sense of rotation may remain in the frontal plane in the presence of a narrow frontal loop (Fig. 3,*A*). The transversal loop, however, shows a negative sense of rotation. In the sagittal plane the QRS loop also rotates in a clockwise direction. It is typical that with left ventricular hypertrophy the T vector loops rotate anteriorly and toward the right. Therefore, we see the T loops coming out of the QRS loops, where they are included normally. This is best seen in the transversal plane. In Fig. 3,*A* the electro- and vectorcardiograms of a case of moderate left ventricular hypertrophy (57-year-old man with moderate hypertension, No. 720) are shown.

It was remarkable to see that in cases with advanced left ventricular hypertrophy, typical changes of the QRS vector loops occur. They turn again more in a vertical plane and their posterior part is lifted upward. So in the transversal plane a clockwise sense of rotation may occur, which is the same as in left bundle branch block. Other characteristics of these two conditions are common, also. Possibly, further studies will throw light on common features of the pathogenesis of advanced left ventricular failure and left bundle branch block. We found that the vectorcardiographic investigation using this new method of lead placement is especially useful in cases of doubtful (beginning) left ventricular hypertrophy. While we have seen that we got false positive results in such cases when using other methods of registration, this was not so when we used the new technique. These false results most probably were caused by an erroneous evaluation of changes of the T waves, which were due to a projection on the horizontal plane. With the use of a transversal plane which comes nearer to the real transversal plane of the heart, such deviations of the T waves toward the right have not been found, except in cases where other characteristics also made a beginning left ventricular hypertrophy possible.

In cases of right ventricular hypertrophy the QRS vector loops show a positive rotation in all three planes. This is demonstrated by the vectorcardi-

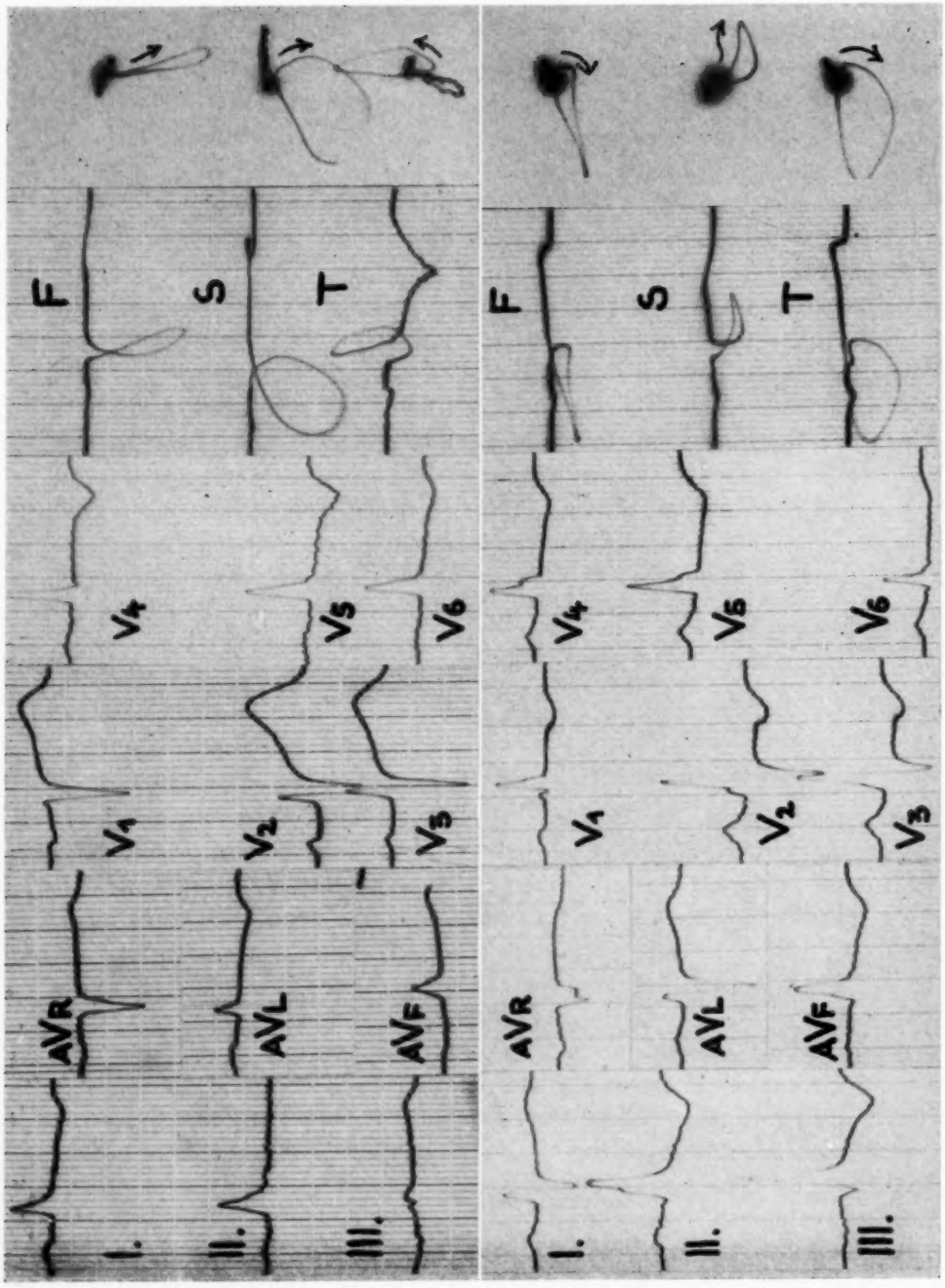
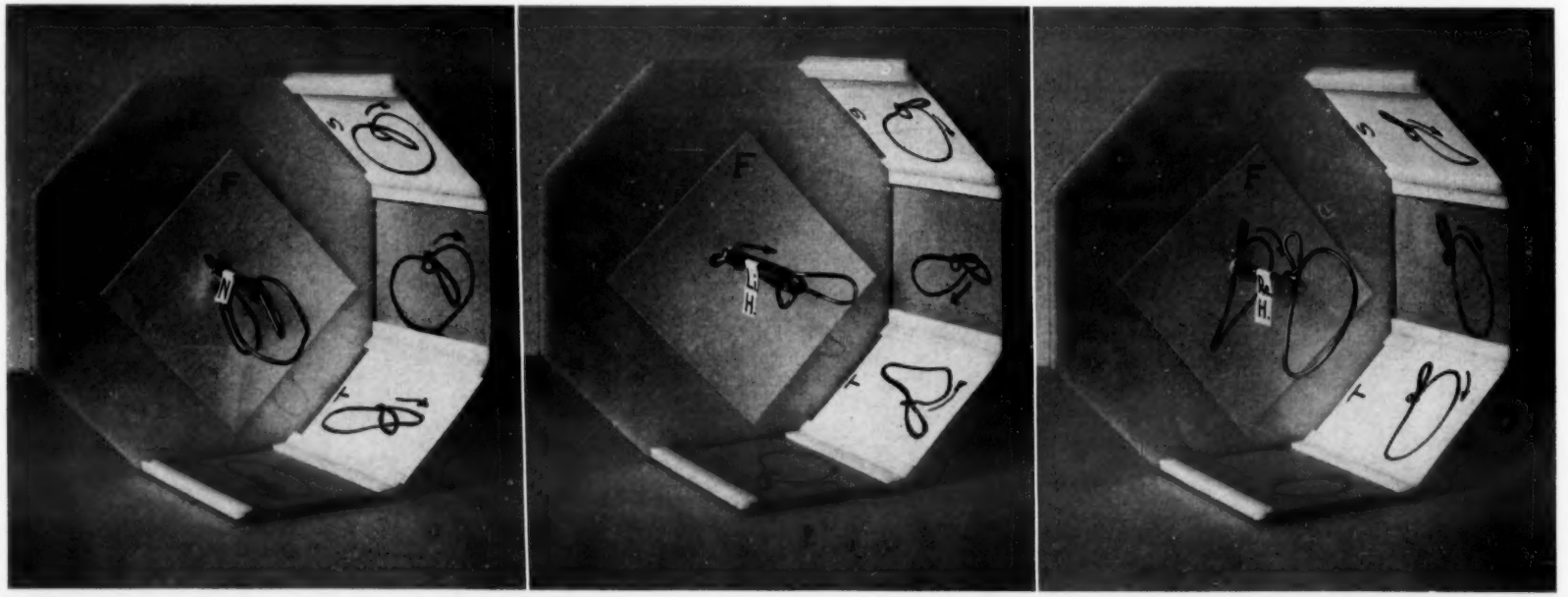


Fig. 3.—*A*, Electro- and vectorcardiograms of a 57-year-old man with moderate hypertension (No. 720). The QRS vector loops are narrow in the frontal and transversal planes. They rotate clockwise in the frontal and sagittal planes, and counterclockwise in the transversal plane. The T vector loops are deviated toward the right and anteriorly and lie outside of the QRS loops. The diagnosis is moderate left ventricular hypertrophy. *B*, Electro- and vectorcardiograms of a 57-year-old woman with slight congenital pulmonary stenosis (No. 224). The diagnosis is marked right ventricular hypertrophy. The QRS vector loops rotate clockwise in all three planes. The T loops are directed toward the left, posteriorly and superiorly, and lie outside of the QRS vector loops.



A. *B.* *C.*

Fig. 4.—Wire models of a normal case (*A*), a case with moderate left ventricular hypertrophy (*B*), and a case with marked right ventricular hypertrophy (*C*) are shown with their projections on the frontal planes (*F*), on the conventional (horizontal) transversal planes (gray), on the transversal planes of the new system (oblique, white, marked *T*), on the conventional (vertical) sagittal planes (gray), and on the oblique sagittal planes of the system described in this paper (white, marked *S*). For the differences of projections on the various planes see text. The frontal vector loops of the new system are obtained if the models are not placed on the horizontal (gray) but on the oblique (white) transversal planes (turning through 45 degrees in a clockwise direction along the anteroposterior axes).

ograms of a 57-year-old woman with slight congenital pulmonary stenosis as diagnosed by heart catheterization and angiocardiography (Fig. 3,*B*). The QRS loops are especially wide in the transversal plane. The T loops lie outside of the QRS loops in all three planes and are directed toward the left, posteriorly and superiorly. In our experience, there were a few cases of definite right ventricular hypertrophy in which the vectorcardiographic QRS loop rotated counterclockwise in the transversal plane when registered by the technique of Polzer and Schuhfried,[4] and clockwise when registered by the technique of Duchosal and Sulzer[1] and by our technique. Thus, we found this method of lead placement to be useful in the detection of cases of right ventricular hypertrophy.

DISCUSSION

A synopsis of the characteristics of our new technique of lead placement is given in Fig. 4. Pictured are three wire models which represent the cases whose vectorcardiograms are shown in this paper. The projections on the usual transversal = horizontal, and sagittal = vertical planes are shown at the inferior and lateral walls of the models (gray background). In the oblique planes (white backgrounds) the projections of our new lead system are presented. Fig. 4,*A* shows normal vector loops. Whereas the projection on a horizontal plane (gray) shows a negative rotation, this is positive in our (oblique) transversal plane (white). The projection of the oblique sagittal plane (white) of the new lead system is wider than that on the vertical sagittal plane (gray) of other lead systems.

Fig. 4,*B* shows the wire model of the case of moderate left ventricular hypertrophy of Fig. 3,*A*. One can see that in the transversal plane of our system (oblique, white) the QRS loop must be narrower than in the horizontal projection (gray). On the other hand, the new (oblique) sagittal QRS projection (white) is wider than the projection on the vertical plane (gray), because the vertical plane is not more or less parallel to the actual plane of the QRS loop as it is in the oblique sagittal plane of our system.

Fig. 4,*C* shows the wire model of the case of right ventricular hypertrophy presented in Fig. 3,*B*. The oblique transversal plane (white) offers a wider transversal projection than the horizontal one (gray). On the other hand, the vertical projection gives a wider loop than the oblique sagittal one (white). With regard to the frontal plane, we should state that the frontal loops as registered by the new system are rotated through 45 degrees toward the right, so that one would see them in correct position if the models were not placed on the horizontal transversal planes (gray) but on the oblique ones (white).

In left bundle branch block the frontal QRS vector loop often displays a triangular form. The transversal QRS vector loop shows a negative rotation. Sometimes in all three planes in cases of right bundle branch block, double loops of QRS are registered; the first part corresponds to the activation of the left ventricle, whereas the second part corresponds to the delayed activation of the right ventricle. The first loop is usually directed toward the left and inferiorly, and the second loop toward the right and anteriorly.

SUMMARY

A new vectorcardiographic lead system is presented. Its characteristic is a better correspondence of its coordinate system to the axes and planes of symmetry of the heart. Therefore, a more accurate registration of the bioelectric changes, especially of hypertrophy of the auricles and ventricles, is possible. Illustrative examples are shown.

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The Spherical Dynamics of the Heart (Myocardial Tension, Oxygen Consumption, Coronary Blood Flow and Efficiency)

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A considerable literature has been devoted to the study of the performance and the energy requirements of the heart. In 1914, Starling and his co-workers[1] had demonstrated that the quantity of coronary blood flow in the heart-lung preparation closely followed changes in the mean arterial pressure. A later study with Visscher[2] called attention to the ventricular end-diastolic volume as a determinant of oxygen consumption. Subsequently, Eckenhoff[3] and Alella[4] established that the volume of the coronary blood flow was dependent on the myocardial oxygen needs.

Evans and Matsuoka[5] calculated the external work of the heart on the basis of the physical formula: work (W) equals aortic pressure (P) multiplied by the volume (V) of the cardiac output:

$$W = P \cdot V \tag{1}$$

The kinetic energy was considered to be negligible. They attempted to estimate the efficiency (E) of the heart in terms of the external work (PV) divided by the best available measure of energy utilization, the oxygen uptake (O_2), so that $E = PV/O_2$. In general, it was found that when the mean arterial pressure was doubled, the oxygen requirement also tended to double. However, doubling of the cardiac output produced a much smaller effect on oxygen consumption. Studies with essentially similar results have been carried out by many workers, using a wide variety of preparations, including the isolated heart,[6,7] the heart-lung,[8,9] the relatively intact animal,[4,10] and on the basis of less secure methods, in man.[11,12] These results, suggesting a lack of equality of "pressure work" and "volume work," raised serious questions concerning the significance of the work formula as a means of gaining insight into the mechanisms of cardiac performance and failure. Numerous attempts have been made to resolve this difficulty.

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Despite its evident inadequacy, many workers[6,7,13-15] have continued to use Equation 1 as the basis of a vigorous controversy on the relationships among arterial pressure, cardiac output, cardiac work, coronary blood flow and oxygen consumption, end-diastolic volumes and pressures, heart rates, residual volumes, and the efficiency of the heart. Some have treated their data in such a way that pressure parameters were designated as "tension,"[15,16] introducing semantic difficulties into the discussion. Perhaps because of the unsatisfactory resolution of the general problem of the pumping action of the heart, the extensive published studies have provided only limited insight into physiologic and clinical problems of heart function.

We have reanalyzed some of these relationships from the point of view that the motion of the heart resembles that of a contracting sphere. When this is done, our data as well as much of that in the literature can be treated in a relatively simple and consistent fashion, permitting a synthesis of previous findings and providing a basis for clinical application. Consideration of the heart as a sphere permits the calculation of its radius, and together with data on pressure, provides quantitative analyses of the tension acting on the heart musculature.

METHODS

We have developed a method[17] which permits the continuous direct measurement of total cardiac output and coronary blood flow, coronary arteriovenous oxygen differences, and blood pressure and heart rate, in an innervated, metabolically normal preparation (Fig. 1). This preparation can be maintained in a relatively steady state without the development of myocardial failure for a minimum of 8 hours.[4,18,19]

Eight dogs, weighing 13 to 31 kilograms, were anesthetized with intravenous pentobarbital sodium.* After thoracotomy at the fourth left intercostal space, positive pressure respiration was maintained at a rate of 20 per minute via tracheal catheter, using the pneophore.†

The azygous vein was ligated, and after heparinization‡ a polyethylene catheter was inserted into the right jugular vein and positioned in the venae cavae so that placement of ligatures completely separated the right atrium from the blood returning via the superior and inferior venae cavae.[17] This venous return was collected in a reservoir from which blood was pumped at a predetermined rate to the right and left pulmonary arteries; the volume of this flow constituted the cardiac output. Under these conditions, the right ventricle received only the coronary venous drainage, which was pumped by it to the pulmonary artery and thence through a rotameter to the reservoir. In our present experiments, Dextran§ was used as a plasma expander. Blood pressures via a cannula in the carotid artery were recorded by means of a Sanborn electromanometer and direct-writing apparatus. Van Slyke determinations of the oxygen content of the coronary venous blood taken from the right ventricle, and of blood from the carotid artery, provided a measure of myocardial oxygen extraction per unit volume of coronary flow.

In some experiments the aortic pressure was elevated to predetermined levels by tightening a screw clamp on the descending aorta. In other tests the left ventricular output was increased at intervals by means of a cannula at the iliac bifurcation, permitting a shunt to pass through a rotameter and join the venous return in the pulmonary arteries. Opening of the shunt had only a minimal effect on the systemic arterial pressure.

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*Pentobarbital sodium was obtained through the courtesy of Dr. John L. Schmidt, Abbott Laboratories, North Chicago, Ill.

†Pneophore: Mine Safety Appliances Co., Buffalo, N. Y.

‡Heparin was obtained through the courtesy of Dr. E. W. Young, The Upjohn Company, Kalamazoo, Mich.

§Dextran was obtained through the courtesy of Dr. Michael G. Mulinos, Commercial Solvents Corp., New York, N. Y.

TABLE I. RESULTS OBTAINED IN A TYPICAL EXPERIMENT*

EXPERIMENT	HEART RATE (PER MIN.)	CARDIAC OUTPUT (ML./MIN.)	STROKE VOLUME (ML.)	RADIUS (CM.)	MEAN BLOOD PRESSURE (MM. Hg)	TENSION BEAT (DYNE/CM. $\times 10^{-3}$)	TENSION MINUTE (DYNE/CM. $\times 10^{-6}$)	O_2 UPTAKE (ML./MIN.)	CORONARY FLOW (ML./MIN.)
7–4†	108	1,402	13.0	1.47	63	46	6.5	10.5	159
7–5	92	1,378	15.0	1.54	110	84	10.1	17.6	299
7–6	108	2,009	18.6	1.66	63	52	7.4	13.8	187
7–7	92	1,495	16.2	1.59	120	96	11.4	19.8	322
7–8	110	1,925	17.5	1.62	53	43	6.1	13.3	178
7–9	92	1,472	16.0	1.58	120	95	11.4	19.0	318
7–10	110	1,916	17.4	1.62	53	43	6.1	12.6	159
7–11†	112	1,448	12.9	1.47	57	42	6.1	11.0	159
7–12	92	1,448	15.7	1.56	120	94	11.2	18.8	318

*All calculations are based on 100 grams of heart weight.
†Control periods.

RESULTS

1. Effect of Aortic Pressure.—Table I shows that increases in aortic pressure produced almost equivalent increases in coronary flow and oxygen uptake, confirming the findings of Starling[2] and other workers.[4-7,15]

2. Effect of Cardiac Output.—Table I indicates that an increase of the left ventricular output by 40 per cent produced increases of 10 per cent in the coronary flow and 26 per cent in oxygen utilization. This finding is similar to results in the literature.[4,6,7,15,18]

3. Effect of Tension.—Examination of our data suggested that the myocardial oxygen consumption might be related to the intraventricular tension. To calculate tension it was necessary to know the intraventricular pressure (P) and its radius (r). The ventricular pressure could be predicted from the arterial pressure. To obtain an estimate of the radius of the ventricular chamber, we made the assumption that at the onset of systole the ventricle resembled a sphere. Woods[20] suggested such a possibility more than 60 years ago in the course of an ingenious analysis of the size of the ventricular chambers. Patterson and Starling[21] also discussed this possibility. If the heart did take on a spherical shape, the radius (r) could be estimated from the relationship: the volume of a sphere (S) is equal to $\frac{4}{3}\pi r^3$. The radius would then equal $\sqrt[3]{S} \div 1.6$. On the basis of these calculations the tension could be obtained, since the tension (T) on the wall of a spherical container equals half the product of the internal pressure and the radius:

$$T = \frac{P \cdot r}{2} \qquad (2)$$

While the heart resembles a sphere only superficially, the data presented below suggest that at least from the dynamic point of view the heart operates remarkably like a contracting spherical structure. We tested our data in order to determine whether the oxygen consumption was proportional to tension.* The formula indicates that doubling of the aortic pressure at unchanged volumes would increase the tension by a factor of 2. The data obtained showed that a doubling of the tension increased the oxygen consumption by 98 per cent (Table I).

Equation 2 indicates that at constant aortic pressure, doubling of the stroke volume should increase the tension by 26 per cent of its control value ($\sqrt[3]{2} = 1.26$). The results obtained showed that the actual oxygen uptake was about half this amount (Table I).

*The calculation of tension, based on per 100 grams of heart weight, was as follows:-

$\frac{P_{mm.\ Hg}}{10} \times \frac{13.6}{1.05}$	$\times\ 1.05 \times 980$	$\times \frac{r_{cm.}}{2}$	$\times$ H. R.	$= T$
Converts $P_{mm.\ Hg}$ to $P_{cm.}$ blood	Converts P to dyne/cm.^{2}	Converts to T in dyne/cm. per beat	Converts to dyne/cm. per min.	

A plot of the myocardial oxygen consumption against the calculated tension (Fig. 2) indicated that ten million dyne per centimeter of calculated myocardial tension was related to an expenditure of about 1.2 ml. of oxygen per minute per 100 grams of heart. The regression line was:

$$\text{Oxygen uptake (ml./min.)} = 1.2 \text{ tension (dyne/cm.} \times 10^{-6}) + 2.6$$

The coronary blood flow was, as expected, related directly to the oxygen uptake, being 23 ml. of oxygen per million dyne per centimeter of tension. The regression line fitting the data for tension and coronary flow (Fig. 3) was:

$$\text{Coronary flow (ml./min.)} = 25 \text{ tension (dyne/cm.} \times 10^{-6}) + 57.$$

4. *Oxygen Utilization at Zero Tension.*—The regression lines indicated that at zero tension each 100 grams of heart required a coronary flow of 57 ml. per minute (Fig. 2), from which it extracted 2.5 ml. of oxygen (Fig. 3). Essentially similar values have been obtained in this laboratory by Kohn[22] on isolated hearts that continue to exhibit normal electrical activity while in mechanical standstill. These values may be related to the energy requirements for activities of the heart not directly involved in the pumping process, such as the maintenance of cellular integrity and electrical activity.

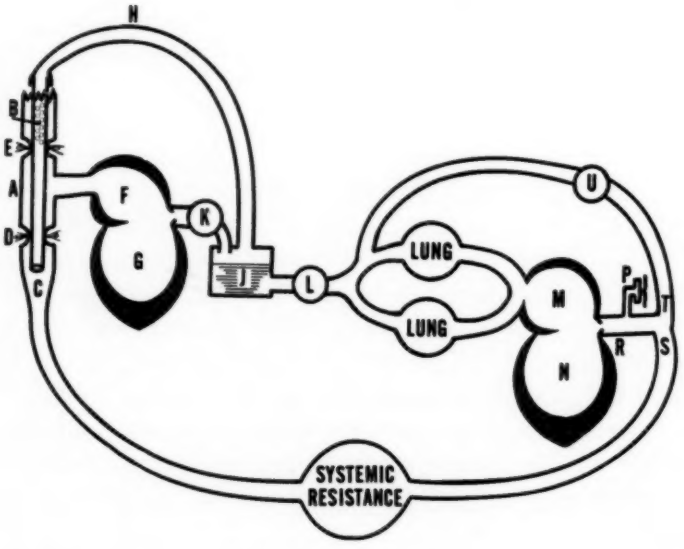

Fig. 1.—Diagram of the system used in the present experiments. Azygous vein (*A*) is ligated, deviating its return to other systemic veins. A catheter (*B, C*) is placed via the right jugular vein into the venae cavae so that placement of ligatures at *D* and *E* completely separates the systemic venous return from the right heart (*F* and *G*). The vena caval blood passes from the catheter (*B, C*) via a tube (*H*) to a reservoir (*J*). The coronary sinus venous return enters the right atrium (*F*), passes to the right ventricle (*G*), and is then pumped via the pulmonary artery through a flowmeter (*K*) to the reservoir (*J*). Blood is taken from the reservoir by means of a metered, constant delivery pump (*L*), which pumps the blood into the two main branches of the pulmonary artery and thence to the lungs for oxygenation. The blood then enters the left atrium (*M*) and ventricle (*N*) and is pumped by the ventricle against an arterial pressure (*P*) registered on a manometer connected to the carotid artery. A screw clamp on the aorta was used to increase the pressure against which the left ventricle had to pump. Blood could leave the aorta via the coronary arteries (*R*), the systemic vasculature (*S*), or a shunt (*T*) with an interposed flowmeter (*U*). The shunt was opened from time to time to increase left ventricular output.

5. *Analysis of Tension Development.*—Calculations of tension must take into account the fact that in each beat the radius of the ventricle decreases as the intraventricular pressure rises. To illustrate this effect (Fig. 4), we have calculated the pattern of tension development in the classical pressure-volume tracings of Wiggers.[23]

With the onset of contraction the ventricular pressure rises sharply from end-diastolic values and very quickly reaches the aortic diastolic level; the ventricular volume remains unchanged during this period of isometric contraction, although the heart tends to assume a spherical form.[20] The tension generated during this period is the integral of the product of the rapidly rising ventricular pressure and of the unchanging radius, the latter being calculated from the stroke output.

Rapid ejection begins as the aortic valve opens, and the radius decreases sharply while the pressure rises more slowly; peak tensions are developed early during this period. The ventricular pressure approaches its maximum in mid-systole, but this occurs at a time when the radius is decreasing rapidly; as a result, the tension falls abruptly and approaches the base line.

DISCUSSION

The present results suggest that myocardial performance and oxygen consumption are determined primarily by the tension in the heart. A. V. Hill[24] showed long ago that the tension produced on contraction of skeletal muscle bore a direct relation to its energy expenditure. There is no reason for thinking that skeletal muscle differs from cardiac muscle in this respect.

Recalculation of published data by many workers who have used isolated hearts or heart-lung preparations[4,5,25] demonstrates a satisfactory relationship between tension and oxygen consumption. We also attempted to recalculate the data of other workers but could not complete these since heart weights and rates were not stated in the original publications. A valid relationship is also shown for available data on coronary flow. These data support our thesis that the tension in the heart is a primary factor in the determination of the myocardial energy requirements measured in terms of its oxygen utilization. They strongly suggest that neurogenic and hormonal factors play a relatively secondary role in the control of internal myocardial energetics. These extracardiac factors may determine heart rate, venous return, peripheral resistance, and to some extent coronary blood flow, and perhaps even the completeness of contraction,[26] but the primary determinant of oxygen utilization and blood flow appears to reside in the geometry of the heart.

Conservation of Tension.—The two ventricular chambers normally eject approximately equal volumes. Since the mean pressure in the normal right ventricle is only about 10 mm. Hg, the tension generated in this chamber is probably only about 10 per cent of the tension in the left ventricle. In our experiments this percentage is even less, since the right ventricle pumps only the coronary blood flow, and this at very low pressures. Therefore, we used only the output of the left ventricle in our calculations. There is further reason to

believe that adequate estimates of oxygen requirements for both ventricles in the normal heart may be obtained from data involving only the left ventricle. Thus, the tension generated by the normal right ventricle provides a mechanical support for the ventricular septum, reducing the force acting on this wall. In a mechanical sense the free wall of the right ventricle may then be considered a part of the ventricular septum, contributing to the strength of this wall and to the left ventricle as a whole (Fig. 5). An advantage in the conservation of tension thus results from having both the left and right hearts in the same spheroid package.

Tension Per Fiber.—The tension on each cardiac fibril changes markedly during the heart beat. This results from the fact that the force on a single fibril is proportional to the total tension at that site, divided by the thickness of the wall. As the heart enters isometric contraction, the tension rises rapidly while the thickness of the heart remains unchanged. With the onset of ejection the tension continues to rise, but now the thickness of the ventricle begins to increase. The maximum force on each fiber is thus reached almost at the onset of the phase of rapid ejection. As ejection continues, the force per fiber falls rapidly. At the end of systole the thickness of the wall becomes maximal, and each fiber has a relatively low tension, but the total is sufficient to enable the heart to accomplish the remainder of the ejection.[20,27]

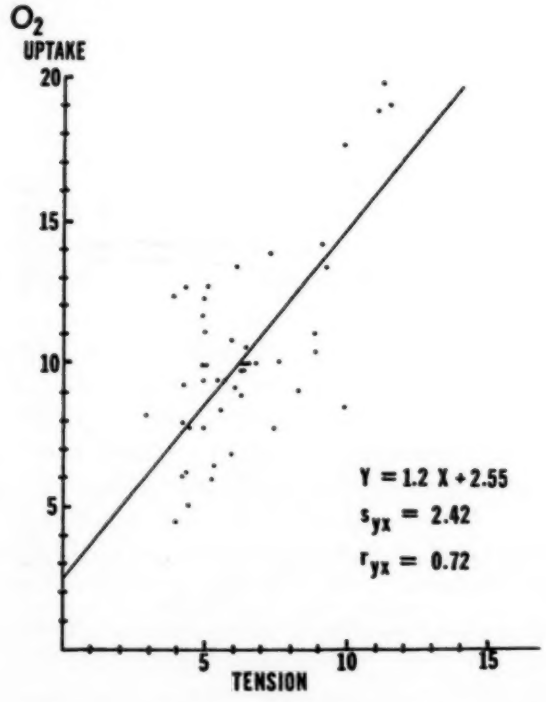

Fig. 2.—Relationship between oxygen uptake (ml./min./100 Gm. of heart weight) and the calculated tension ($T = \frac{P \times r}{2}$) in dyne/cm. x 10^{-6}. The line represents the regression line expressed by the equation; S_{yx} is the sample standard deviation from regression, and r_{yx} the sample correlation coefficient.

The foregoing analysis permits re-examination and systemization of physiologic data on myocardial performance and oxygen consumption, and permits their interpretation in certain clinical conditions. A few of these are discussed briefly.

High Intraventricular Pressures.—The ventricular pressure is increased in arteriosclerosis, hypertension, and aortic stenosis. In generalized arteriosclerosis the diastolic pressure is often normal, but the myocardial tension is elevated as a consequence of the higher peak systolic pressure. By contrast, in diastolic hypertension the ventricular pressure rises to abnormal values even before ejection begins; the tension during this isometric period is therefore enhanced even at normal heart volumes. If the heart volume were increased significantly, the tension would be even greater, in proportion to the change in radius. As ejection begins, the pressure continues to rise to higher values while the radius falls off, but not so sharply as in normotension. The total tension of each beat is thus markedly increased, requiring an equivalent increase in coronary flow and oxygen uptake.

An even more marked pattern of increased tension and oxygen demand appears in aortic stenosis, wherein the ventricular pressure rises to very high levels while ejection is delayed. The maximal product of the pressure and the radius under these conditions may be very high.

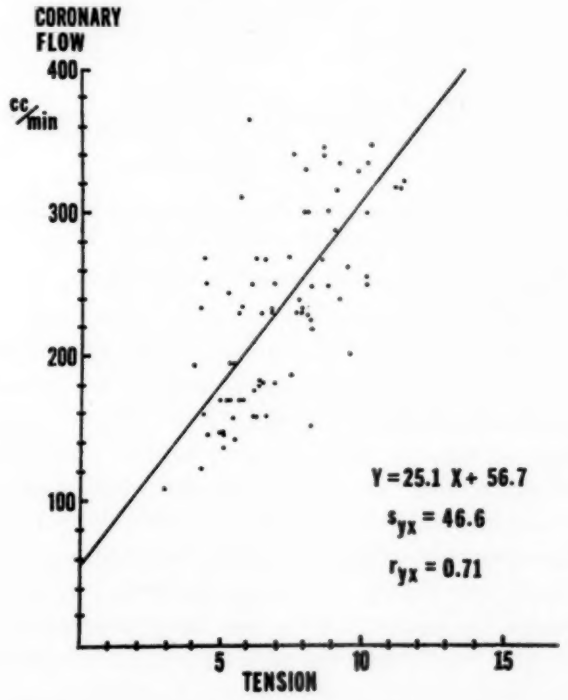

Fig. 3.—Relationships between coronary blood flow (ml./min./100 Gm. of heart weight) and the calculated tension ($T = \frac{P \times r}{2}$) in dyne/cm. x 10^{-6}. The line represents the regression line expressed by the equation; S_{yx} is the sample standard deviation from regression, and r_{yx} is the sample correlation coefficient.

In the foregoing instances the high tensions are usually associated with, and may participate in, the induction of ventricular hypertrophy. Not only would the left ventricle be expected to hypertrophy under these conditions, but the free right ventricular wall, which, as mentioned above, apparently contributes to the support of the ventricular septum by having an increased tension transmitted to it, would also tend to increase in thickness. Such hypertrophy of the free right ventricular wall is a common, unexplained finding in apparently isolated left ventricular overload.[28]

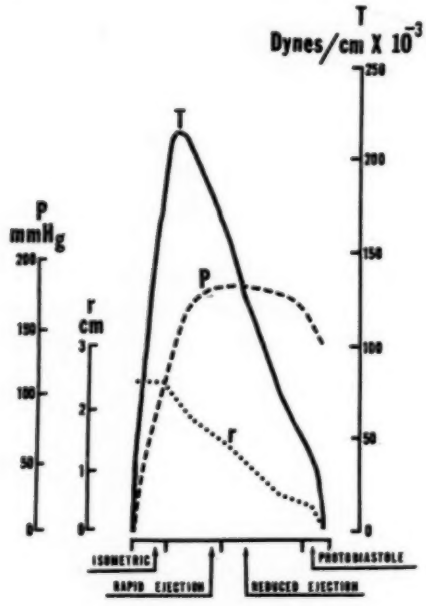

Fig. 4.—Pattern of tension development as calculated from the classical pressure-volume tracings of Wiggers,[23] where P is the intraventricular pressure and r is the radius calculated from the ventricular volume ($r = \frac{\sqrt[3]{3V}}{4\pi}$), and T is the calculated tension. (See text.)

Thickening of the wall would reduce the tension on any single muscle fibril, but the total tension, and possibly the myocardial oxygen requirements, would not necessarily be affected by such hypertrophy. The increased thickness of the ventricular wall also acts as an impedance to inflow, thereby tending to reduce the end-diastolic volume and the cardiac output. This effect would lower the tension somewhat and permit compensation in a low-output state.

Low Ventricular Pressure.—When vascular collapse supervenes and the blood pressure and cardiac output fall, the intraventricular tension may be at very low values. It might be expected that the oxygen requirements of the heart would decrease proportionately, but the perfusing pressure for the coronary vessels is also reduced. This situtation may be met by the physiological coronary arteriolar dilatation which appears to be regulated to a considerable degree by intrinsic myocardial mechanisms.

Increased Ventricular Volumes.—In hypermetabolic states, such as hyperthyroidism and pregnancy, in the presence of mitral or aortic insufficiency or an

arteriovenous shunt, increased stroke outputs take place with only slight effects on the ventricular pressure. This effect is partially compensated by reduced pressure at the onset of ejection. Unless the stroke output is increased several fold, the increase in the total tension on the heart may be only moderate. The exact effects may be expected to differ according to the differences in the cube roots of the stroke outputs.

In mitral insufficiency the tension will tend to increase in proportion to the cube root of the volume during each stroke. However, since regurgitation begins early during systole, prior to the onset of aortic ejection, the rapid reduction in radius would have the effect of reducing the tension early in this period.[29,30] As a result, peak ventricular tensions may be normal.

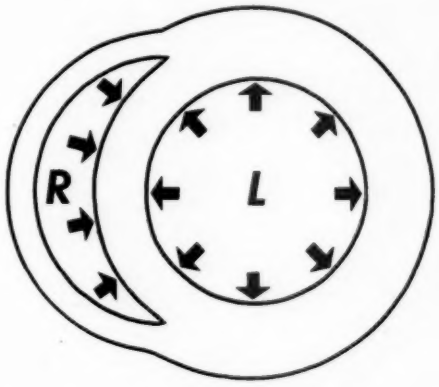

Fig. 5.—An illustration of conservation of tension, whereby the free right ventricular wall supports the septum and contributes mechanically to the strength of the left ventricular wall.

The low diastolic pressure in aortic insufficiency would tend to reduce the tension somewhat during the period of isometric contraction. However, the ventricular filling may be several times greater than normal, and the systolic pressure tends to be high, with both factors increasing tension. The sum of these tendencies may impose a significantly increased load on the heart and heighten oxygen requirements. The situation may be further aggravated by the fact that the coronary flow may be limited by the low diastolic pressure.

Decreased Ventricular Volumes.—In severe mitral stenosis or in cachexia the reduced filling of the ventricle would be expected to shorten the radius and thus lower the total tension and the oxygen requirements of the heart.

Residual Volume.—The normal heart has a small residual volume at the end of the ejection period.[31] A residual volume of greater proportions, as occurs in heart failure, can be expected to increase the ventricular volume at the onset of systole, the tension, and the oxygen requirements, without change in cardiac output.

Thus a residue of 10 per cent of the stroke output would increase the tension and the oxygen consumption by only about 3 per cent, while a residual volume of 100 per cent would increase the tension by nearly a third. The cost of various residual volumes, calculated on the basis of increased tensions, is given in Fig. 6.

These calculations suggest that myocardial failure with the development of a significant residual volume would raise the ventricular tension and oxygen requirements, without contributing to output; the result would be a significantly diminished efficiency of the heart. Elimination of this residue, as by phlebotomy, may increase the efficiency of the heart on the basis of a simple alteration of its geometry, by reducing the radius and thus its tension and oxygen requirements.

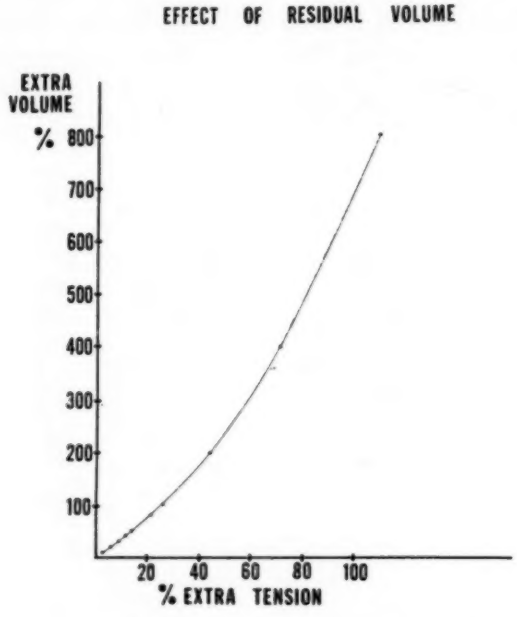

Fig. 6.—Cost of various residual volumes calculated on the basis of increased tensions.

Efficiency.—A considerable controversy has raged over the estimation and significance of calculations of cardiac efficiency in normal and in decompensated hearts.[2,5-7,11,12] Attempts to resolve this problem have generally met with failure, since "pressure work" was very costly in terms of oxygen utilization, while an apparently equivalent "volume work" somehow required a much smaller amount of oxygen. Our correlation between cardiac oxygen consumption and a parameter including both pressure and the cube root of the volume helps to clarify certain questions related to the efficiency of the heart.

Analysis of the mechanics of a contracting sphere suggests that a heart operating in this manner will have greater efficiency as its stroke volume increases, provided the residual volume is minimal. This is seen from the relationships:

$$\text{Relative Efficiency} \propto \frac{Work}{O_2} = \frac{PV}{O_2} \propto \frac{PV}{T} \propto \frac{PV}{Pr} \propto \frac{V}{r} \propto \frac{r^3}{r} \propto r^2$$

It is of particular interest that this relationship indicates that the pressure against which the heart works has little effect on its efficiency.

Myocardial Infarction.—The deleterious effects of myocardial infarction would appear to result in part from the tendency to an increased residual volume and radius, especially if an aneurysm is present, but also to be based on the fact

that the infarcted area can no longer participate actively in the equal distribution of the tension on the spheroid ventricle. A disparity in the tension vectors at the site of infarction may be expected to result, with a disturbed development and distribution of tension throughout the three dimensions of the heart.

GENERAL DISCUSSION

The present analysis of myocardial oxygen consumption and coronary flow in dogs permits a new approach to the study of the cardiac pumping mechanism. Consideration of the heart as a contracting sphere permits the estimation of ventricular tension, since its apparent radius may then be calculated from the stroke output. The oxygen consumption of the heart is correlated with a factor which includes both volume and pressure. The equivalence of pressure loads and volume loads may thus be demonstrated, provided the volume is first translated into radius.

The deleterious effects of a residual volume of blood in the heart may be shown to be related to the geometry of the pump rather than to disorders of myocardial metabolism. The analysis also indicates that the relative efficiency of the heart is related to the square of its radius, provided residual volume is minimal. Deficiencies in myocardial infarction are seen as depending in part on a distributed distribution of the vectors of myocardial tension.

Spherical pumping mechanisms and their special relationships of pressure and radius are not limited to the heart. The gravid uterus is apparently able to exert more force on its contents after its radius is decreased subsequent to rupture of the amnion, as Woods[20] noted long ago. It may be suggested that similar mechanisms participate in the expiratory difficulties of patients with emphysema, since increases in both intrapulmonary air pressure and radius would apply an excessive tension to the chest wall and impede the muscles of active expiration from expelling the trapped air.

Application of the principle outlined above provides a new approach to the mechanical burden on the heart and to its demand for coronary blood and oxygen. Some physiologic and clinical implications of this approach to cardiac energetics are discussed.

SUMMARY

Pressure work of the heart has long been known to be more costly in terms of myocardial oxygen consumption and coronary blood flow than an apparently equivalent volume work. This problem was restudied in the dog.

Pressure work and volume work were shown to be equivalent when the analysis was carried out from the point of view that the heart behaved like a contracting sphere. Oxygen consumption was then dependent on intramyocardial tension, this being calculated as half the product of the intracardiac radius and pressure. Recalculation of cardiac performance in a number of reports in the literature showed that previously contradictory data could be resolved by this relatively simple relationship. The bases for this type of analysis and a number of physiologic and clinical aspects of cardiac function are discussed.

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Graphic Recording of the Korotkoff Sounds

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For years, clinicians, physiologists, and pharmacologists have felt the need for a simple, inexpensive method of obtaining systolic and diastolic blood pressure indirectly and over long periods in man and the larger laboratory animals. Many ingenious instruments, both automatic and manual, have been devised which aimed at providing these data. Of all of the techniques used in these investigations, the auscultatory method has been the most readily accepted. However, utilization of the Korotkoff sound method presents its own difficulties, for it is often difficult to apply the technique to man and to animals, large and small, in inaccessible environments and in the presence of high ambient noise. Nonetheless, the method can be used, and, of late, many graphic recording instruments have employed the auscultatory method to determine blood pressure without arterial puncture. It is the purpose of this paper to examine the basis of this technique and describe a simple application of the auscultatory method used with routine success in this laboratory for the past three years.

That the Korotkoff auscultatory method yields pressures which are, for practical purposes, very close to direct blood pressure is well established. Many investigations have been carried out in which arterial pressure was recorded while the auscultatory method was applied. From these, extending from 1905 to 1939[1] and 1951,[2] the reliability and limitations of the method have been adequately documented. In the latter years two international committees, representing the American Heart Association and the Cardiac Society of Great Britain and Ireland, set up a standardized procedure, defined the "end points" for reading the cuff pressure, and indicated the accuracy obtainable using these end points. In essence, they divided the spectrum into four phases of sound and an additional one of silence. As the pressure in the cuff is lowered from above suspected systolic pressure, while monitoring the sounds over the brachial artery at the antecubital space, the appearance of the first sound, signaling Phase I, is used as systolic pressure. As the cuff pressure is lowered further, the sound changes in intensity and character, becoming softer (Phase II), then increases

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in intensity and often in frequency (Phase III), suddenly becomes dull (Phase IV), and usually disappears (Phase V). The cuff pressure when the sounds cease is read as diastolic, or if they do not cease, the pressure at which sudden dulling occurs is to be taken as diastolic pressure.

From a very large series of observations on normal subjects, Goodman and Howell[3] give the average width of the pressure phases as 14, 20, 8, and 6 mm. Hg. Swan,[4] in his extremely comprehensive investigation, differed on the width of Phase IV, placing it at 14 mm. Hg. Of all the phases, the width of the fourth is the most controversial, since often there may be no fifth or silent phase. Another phenomenon sometimes occurs, called the auscultatory gap, in which Phase II is silent. Therefore, care must be exercised in making readings in order to avoid confusing Phases II and V.

Using the criteria described, the 1951 committee, in addition to making recommendations on techniques, reported that the pressure read as systolic is approximately 3 to 4 mm. Hg too low, with a scatter of ±8 mm. Hg. In the case of diastolic pressure, if Phase IV (muffling) is used, the reading places diastolic pressure 8 mm. Hg too high; for this reason, Phase V (silence) is recommended whenever possible.

With limited regard to the frequency spectrum, the sounds have been used in a variety of ways, being either presented graphically or to control automatic recording devices which cycle cuff pressure to the appearance or disappearance of the sounds to read either systolic or diastolic pressure. In 1936, Omberg[5] described the use of the latter type of device, while Gilson, in 1941[6] and 1942,[7] used the former technique to produce a two-channel graphic record of cuff pressure and auscultatory sounds. A new device, similar in principle to Omberg's, was described recently by Gilford and Broida[8]; it produced a dotted graphic record of systolic and diastolic pressures, each pair of dots representing a sampling cycle. Records taken with this instrument were published by Rose and associates.[9] Quite recently, an ingenious instrument somewhat similar to Gilson's and to that in use in this laboratory was described by Currens and associates.[10] These instruments will be discussed later in this report after further development of the characteristics of the auscultatory method.

It is difficult to find quantitative physical data relating the cuff pressure and the frequency of Korotkoff sounds in the various phases. However, scattered through the literature such information exists, the most pertinent of which follows.

As long ago as 1914, Hooker and Southworth[11] recorded the Korotkoff sounds. In their study, a carbon button microphone was employed to detect the feeble sounds and they were displayed by a Lippmann capillary electrometer. This instrumentation displayed a predominant frequency of around 15 cycles per second. Eleven years later, Bramwell and Hickson[12] used a Frank capsule to record photographically the sounds from under an occluding cuff, but were unable to detect differences in wave form in the different phases. However, they did record low-amplitude auscultatory sounds having frequencies as high as 100 to 150 cycles per second. A very intensive investigation was carried out in the following year by Korns,[13] who made some 1,500 recordings of the auscul-

tatory sounds. Employing a membrane manometer, he found sounds at frequencies of 40 to 256 cycles per second. Of these, only 2.5 per cent were above 250 cycles per second.

More recently, Groedel and Miller[14] made a graphic study of the auscultatory sounds, using a heart sound pickup to detect the sounds and an electrocardiograph (photographic) to reproduce them. The prominent frequencies in their recordings taken from normal subjects are in the range of 45 to 60 cycles per second. In the case of a 65-year-old hypertensive patient (blood pressure, 200/90 mm. Hg), the frequency of the sounds was higher, extending from 60 to 140 cycles. In a similar investigation, Rappaport and Luisada[15] used a special pressure-equalized microphone to record the sounds on a photographic electrocardiograph, during the four phases. These records, when enlarged, revealed frequencies of from 25 to 55 cycles per second. Gilford and Broida, using the auscultatory signals as control information in their automatic blood pressure recording instrument, adopted a frequency band-pass filter having 40 per cent attenuation at 40 and 200 cycles per second in order to select only the useful auscultatory information.

The sounds recorded with the largest amplitude in all of these studies are low in frequency. Aural monitoring gives the impression that the sounds are higher in frequency. However, it must be remembered that it is the harmonic content that gives a sound its characteristic quality, and a close inspection of the recorded auscultatory sounds shows that there are high-frequency components present in very minute amplitude, as well as steep wave-fronts on some of the lower frequency sound pulses. For faithful reproduction of the auscultatory sounds the pass-band should be considerably wider than that necessary to pass only the principal frequencies. Predominant complex waves of 25 to 50 cycles seen in the recordings require a band-pass of several times these frequencies to fully amplify the harmonics and preserve the character of the sounds. Perhaps a conservative estimate would be to amplify up to the third or fourth harmonic. This would then define the auscultatory sound spectrum from approximately 25 to 200 cycles per second. However, for practical purposes, if the sounds are used as "end points," loss of the small amplitude higher frequency components detracts little from the accuracy of the measurement. Therefore, acceptance of a narrower band width is permissible if the sounds are used for purposes of indication.

Little if any definite information is available on the absolute intensity of the Korotkoff sounds. Like all biological signals detected at a distance from their origin they are small in amplitude. Furthermore, when detected stethoscopically, the combined frequency response of the stethoscope[16] and the decreasing auditory acuity with progressively lower frequencies both conspire to make it difficult to quantitate their intensity. However, graphic records of the sounds do demonstrate intensity differences which can be used to synthesize a diagram which illustrates the main characteristics of the auscultatory method. Fig. 1 summarizes the pertinent data on the normotensive subject, compiled from records published by the authors cited.

The sequence of events, starting with above systolic cuff pressure and slowly reducing it, is as follows. No sound is heard until the cuff pressure falls just below systolic pressure. This event ushers in Phase I. The principal sounds heard have frequencies of 40 to 55 cycles per second. From the beginning of Phase I the intensity increases but the frequency may fall. Phase II is ushered in by the addition of higher frequencies at first; then, toward the end of the phase the frequency drops, while the peak intensity of the sounds varies only slightly or diminishes throughout the phase. As Phase III arrives, the intensity climbs abruptly and higher frequencies are added. As Phase IV arrives, both frequency and intensity drop sharply, and disappear in Phase V. The auscultatory gap, if it occurs, is shown dotted on the figure.

In the creation of a system to yield systolic and diastolic pressure two channels of data are required, one the cuff pressure, the other the Korotkoff sounds. Simultaneous presentation of these two channels, each suited to the type of information they are to portray, can constitute a system for the indirect measurement of blood pressure. The range of the pressure channel need not cover more than 0 to 300 mm. Hg, and for practical purposes an auscultatory channel covering a band width of 25 to 80 cycles per second, with some frequency response past 100 cycles per second, is adequate to reproduce the sounds in hypertensive subjects.

There is little difficulty in recording cuff pressure, but considerable difficulty is encountered in providing an auscultatory channel free of artifacts. Various methods have been used to detect the feeble, low-frequency auscultatory sounds. Omberg and Gilson detected the sounds with crystal microphones applied over the brachial artery at the antecubital fossa. Gilford and Broida developed their own contact microphone from a Fleischer diaphragm stethoscope receiver (1-1/2 inches circular by 5/16 inch thick). To detect the sounds with more efficiency they employed the technique used by many anesthesiologists, namely, slipping the receiver under the lower edge of the cuff. A similar method was used by Currens and associates, who inserted their microphone (32 by 9 mm.) into a pocket sewn into the lower edge of the cuff. Rappaport and Luisada used a pressure-equalized crystal microphone pneumatically coupled to a second cuff below the main occluding cuff.

The sounds detected by these methods were amplified and used in various ways. In Omberg's instrument the cuff pressure was regulated to obliterate Phase I auscultatory sounds. A mercury manometer recording of cuff pressure graphed systolic pressure. Gilson, on the other hand, used a low-frequency recording milliammeter to show cuff pressure while the sounds were presented on the lower edge of the record by a rapidly responding stylus driven by a dynamic loud-speaker movement. Gilford and Broida did not reproduce the sounds directly, but used them to control solenoids connected to pressure gauges, one of which opened and closed at systolic pressure and the other at diastolic. In this way panel meter readings indicated systolic and diastolic pressures. At the same time these readings were marked by dots on a recording chart. Currens and associates converted the sounds electronically to pulses of longer duration, the amplitude of which was proportional to the intensity of the original sounds.

This technique permits the use of a slowly responding recording milliammeter to display cuff pressure and the electronically "stretched" sound pulses at the expense of complexity of electronic circuitry, and is unnecessary when rapidly recording pens are available. The data presented here illustrate that the normal Korotkoff sounds are well within the range of the frequency response of most good quality recorders. In this way the single-channel record of cuff pressure and superimposed pulses revealed systolic and diastolic pressures. Rappa-

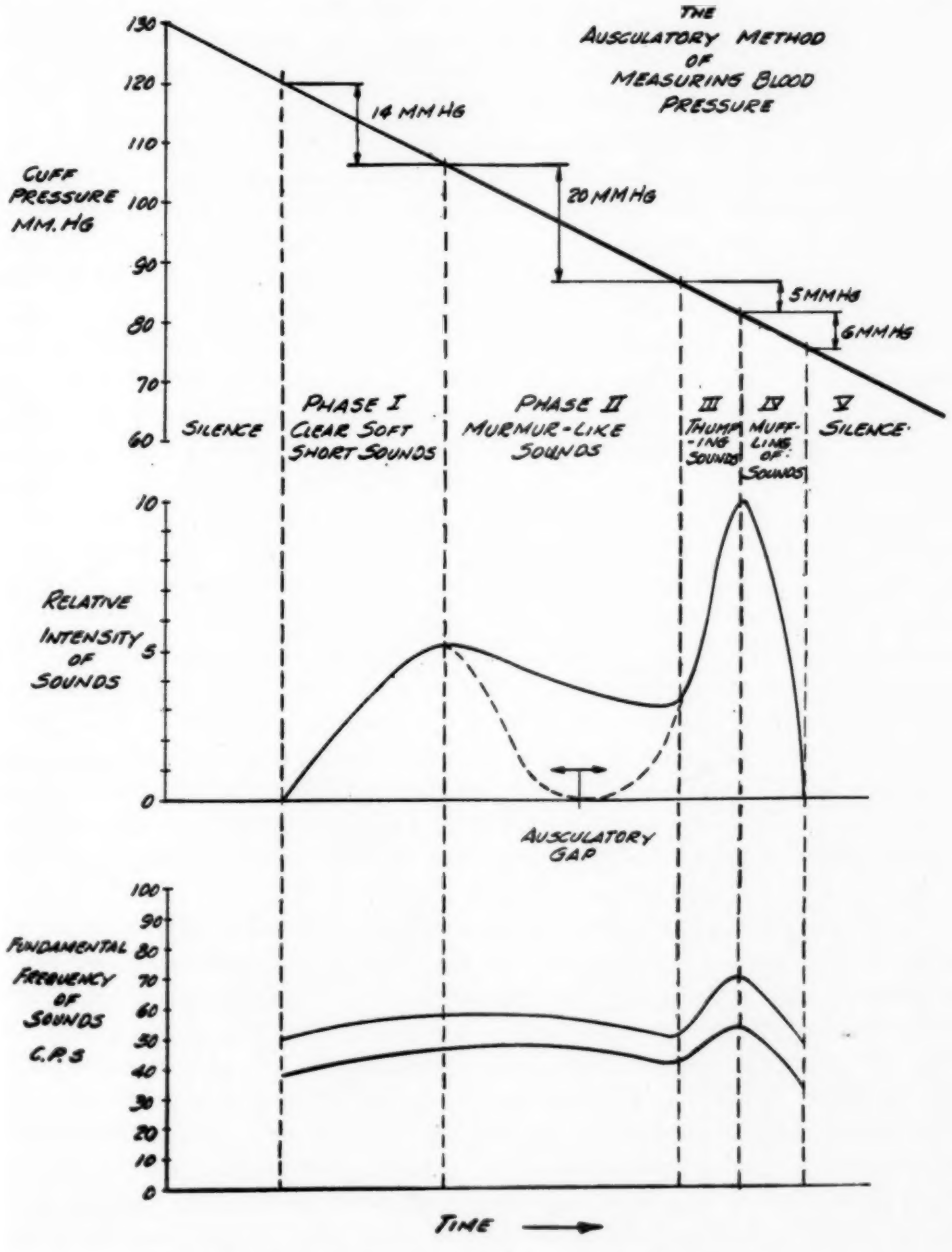

Fig. 1.—The auscultatory method of measuring blood pressure.

port and Luisada reproduced the sounds on a galvanometer electrocardiograph and identified cuff pressure on the same record.

All of the equipment described has tended to be complex and, hence, costly. Probably the largest factor contributing to the complexity is the size of the auscultatory sounds themselves. Gilford and Broida and Currens, by placing the microphones under the cuff, found that the sounds were much louder, yielding a better signal to noise ratio for the system. On the other hand, by placing microphones of appreciable size under the cuff, some may feel, on theoretical if not on practical grounds, that such objects may compress the artery, even with the cuff deflated, and distort the measurement. The authors do not report any practical difficulties from this procedure.

Experience in this laboratory has confirmed what many investigators have found, i.e., the nearer to the cuff the more intense the sound, and immediately under the middle of the cuff the sounds are loudest. Investigations have also shown that if a microphone is to be placed under the cuff to detect the sound, it must be of the smallest dimensions in order to prevent occlusion of the artery even with low cuff pressures.

Accordingly, a combined cuff-sound detector unit was designed in which a miniature acoustic pickup was installed. This detector consisted of a small (7 by 17 by 1 mm.) piezocrystal mounted in the cloth sleeve of the cuff and located in the distal third. The crystal unit was obtained from an inexpensive phonograph cartridge. The crystal was first fitted with a light, flexible, shielded cable, and then a layer of aluminum foil for shielding was added. Finally, the unit was dipped in Insul-X varnish and allowed to dry. When dry, it was permanently mounted into the cuff in the manner described and illustrated in Fig. 2,*A*.

Because the pickup is in such a favorable position to detect the sounds, and the piezocrystal is an efficient converter of sounds to an electrical signal, very little amplification is required for their reproduction. Moreover, since the cuff pressure varies slowly during deflation, a relatively inexpensive pressure transducer can be used to provide an electrical signal proportional to cuff pressure. Because the frequency spectrum of both events falls within the capabilities of good quality graphic recording pens, a very simple system can be synthesized to record blood pressure using the auscultatory method.

A simple sound preamplifier pressure-transducer unit, the electrosphygmograph (ESG) (Fig. 2,*B*), was constructed, which when connected to the cuff for pressure and the crystal cartridge for sound, produces a combined output signal superimposing the auscultatory sounds on the cuff pressure. A single stage of push-pull amplification for the sounds and a photoelectric Burbon tube pressure transducer produce signals large enough to require only a two-stage direct-coupled amplifier to drive the recording pen. The particular amplifier (Fig. 2,*C*) used in this laboratory is the Physiograph power amplifier[17,18] which is similar to the last two stages in most modern electrocardiographs. The recording pen (Fig. 2,*D*), having a frequency response between conventional electrocardiographic and electroencephalographic recorders, is also a part of the Physiograph recorder.

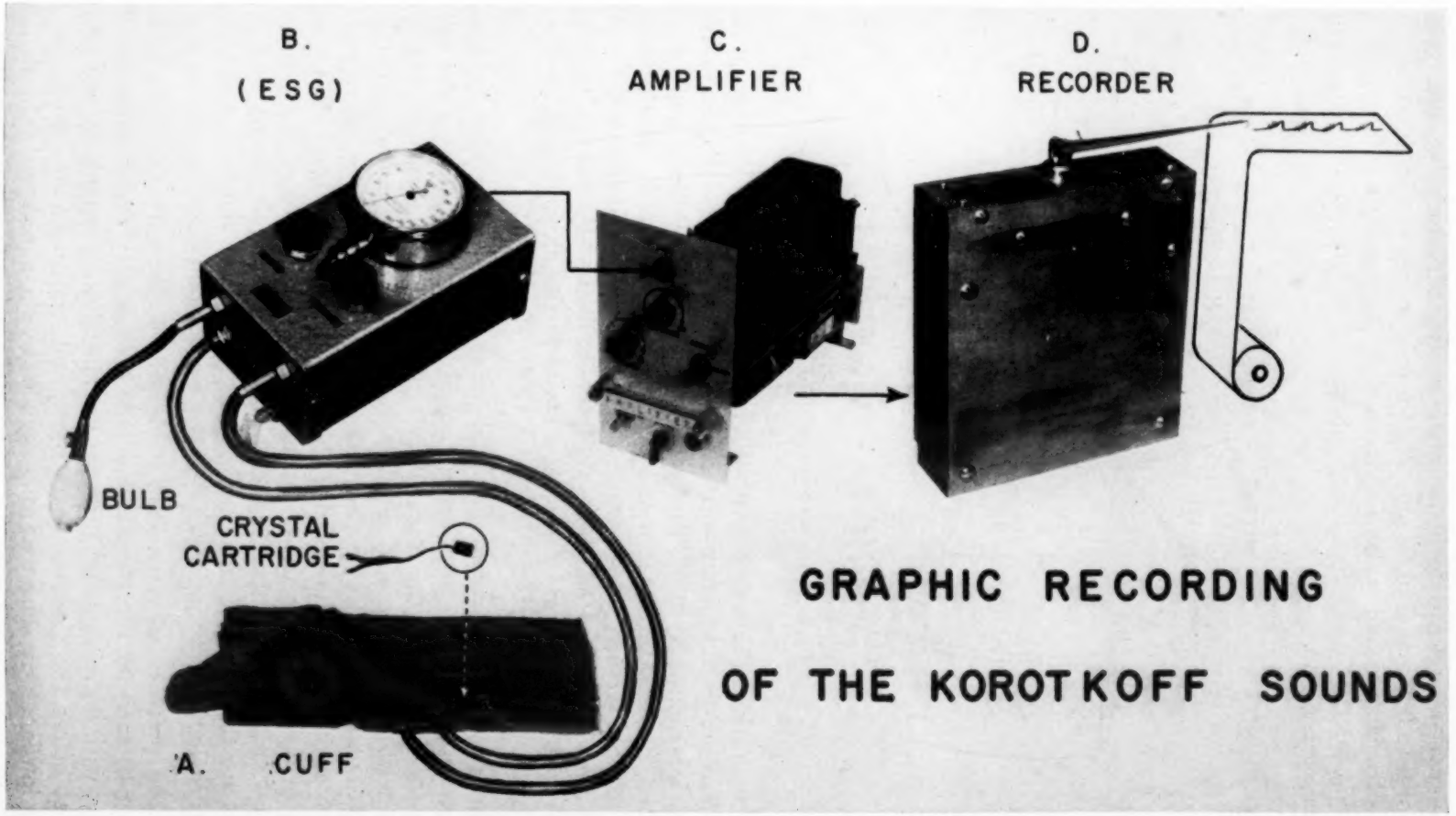

Fig. 2.—The components of the system. *A*, Cuff. *B*, Electrosphygmograph. *C*, Power amplifier. *D*, Recording pen.

The over-all operating characteristics permit reproducing cuff pressure ranges of 0 to 300 and 0 to 50 mm. Hg for four inches of pen deflection. The effective frequency band width for the auscultatory sounds is 15 to 50 cycles per second for the 70 per cent amplitude points and 10 per cent amplitude at 100 cycles per second.

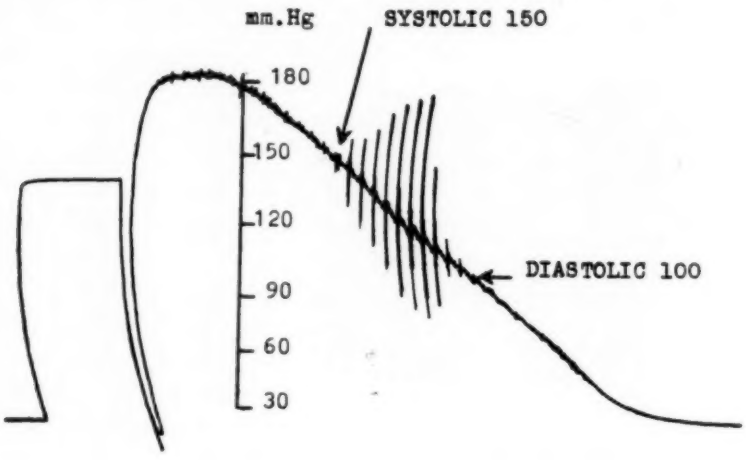

Fig. 3.—Typical record obtained on a human being.

In operation, the cuff is installed in the conventional manner, with the sound detector distal to and over the compressed artery. As the cuff pressure is reduced from above systolic, the recording pen falls. When systolic pressure is reached, the sounds appear as spikes on the graphic record. As the cuff pressure is reduced further, the sounds change in amplitude and frequency, reaching a maximum in Phase III, falling abruptly in Phase IV, and disappearing in Phase V. A typical record taken on a normotensive human being is shown in Fig. 3.

The test of a system cannot be made on the basis of normal subjects alone. The merits of a system are best portrayed by its capabilities under adverse circumstances. One of the most difficult blood pressure measurements is that made on laboratory dogs and small children. Using a standard pediatric cuff (7.5 cm. in width) fitted with the miniature sound pickup, the record of Fig. 4 was obtained on a morphinized dog (10 Kg., left brachial artery) with a ligated branch of the coronary arteries. In this figure the top record is electrocardiographic Lead II, below that is the electrosphygmographic record, and at the bottom are the 5-second time marks. In spite of the multiple ectopic beats, there is little difficulty in identifying the systolic and diastolic end points.

Blood pressure measurements made graphically with the ESG while an observer listened for the Korotkoff sounds show a very close correlation. Frequently, with decreasing cuff pressure the auscultatory sounds appear graphically just before the observer hears them, and, similarly, they often last to a slightly lower cuff pressure than that signaled by the observer.

The method works well on animals, and many comparisons have been made on anesthetized dogs in which carotid end pressure was compared with the pressure determined using the ESG on a brachial artery. The results of a series of these determinations largely confirmed the data set forth by the 1951 committee, with the exception of the fact that systolic pressure tends to be approximately 10 per cent higher while diastolic pressure is usually identical.

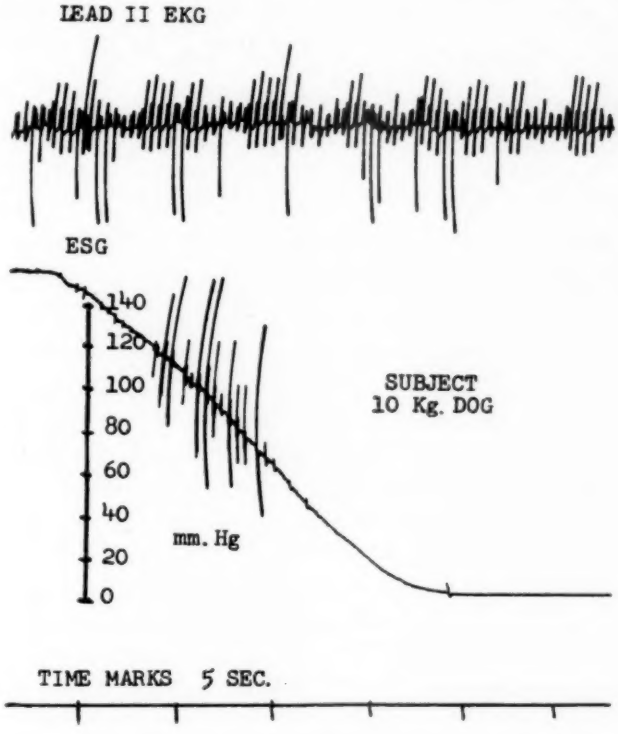

Fig. 4.—Typical record obtained on a dog.

In our hands one of the really practical uses of this instrument has been the making of blood pressure measurements on subjects in inaccessible environments, such as on patients in an iron lung. It is also of considerable value in obtaining blood pressure measurements on subjects exercising mildly, and on unanesthetized dogs. Since the sound pickup is located in close proximity to the origin of the sounds, extraneous noises such as those due to the cycling of an iron lung or slight somatic movements create minimal artifacts in the recording. One additional practical feature is the fact that only one object need be attached to the subject. This is especially valuable when long-term blood pressure measurements are to be made on subjects in inaccessible environments.

SUMMARY

The characteristics of the auscultatory method are analyzed in terms of predominant frequencies in the various phases. The data demonstrate the appropriateness of employing graphic methods for inscribing these sounds directly

superimposed on a record of occluding cuff pressure. A simple instrument using this principle is described and its usefulness demonstrated in man and laboratory animals.

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The Prognosis in Essential Hypertension

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Both when referring to life insurance and when judging the significance of the different forms of therapy in connection with the long-term prognosis in essential hypertension, it is important to know as much as possible about the prospective length of life postulated for an untreated group of hypertonics.

Many earlier investigations included some cases of secondary hypertension, particularly kidney diseases, which can influence adversely the prognosis. The investigations of Janeway,[1] Hamman,[2] and others[3,4] show, for the above reason, a mortality of 70 to 80 per cent (Table I). The investigations made in later years[5-11] are, in most instances, free of individuals suffering from secondary hypertension; hence, the death rate is correspondingly low.

TABLE I. A SURVEY OF SOME PROGNOSTIC STUDIES OF INDIVIDUALS WITH HIGH BLOOD PRESSURE

INVESTIGATORS		NUMBER OF PATIENTS	YEARS OF OBSERVATION	DEAD (%)
Janeway	(1913)	458	10	75
Topp	(1919)	157	2– 5	83
Benni	(1926)	148	4	77
Hamman	(1928)	778	10	78
Blackford	(1930)	222	5–11	50
Rosling	(1934)	450	8	30
Bechgaard	(1946)	1,038	4–11	28
Frant	(1950)	418	8– 9	32
Storm Mathisen	(1951)	290	10	33
Bechgaard	(1954)	1,038	16–22	57

Most investigations suffer from the fact that some of the patients may have had their blood pressure symptoms several years before registration. This can be avoided partly by lowering the age range at registration as much as possible,[12] for example, to 45-46 years,[9,10] and by reckoning that those that show symptoms of essential hypertension have not had them long.

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OWN MATERIAL

The material consists of patients who were treated in several medical departments in Oslo before 1944, for different ailments, and in whom essential hypertension was discovered casually. The patients had had no special treatment for their hypertension.

The group consists of patients who were under 46 years of age at the time of the registration. The mean age on registration was 38 years for the women and 37 years for the men. Most of the patients were over the age of 35 when first examined.

The patients included in the material were found to have a maximum systolic blood pressure of 160 mm. Hg or more, or a maximum diastolic blood pressure of 95 mm. Hg or more.

There was a total of 290 patients, of whom 179 (62 per cent) were women, and 111 (38 per cent) were men (Table II).

This group of patients was recalled for examination several times. In 1950-51, it was found that 52 women (29 per cent) and 46 men (41 per cent) had already expired; this mortality was primarily the result of hypertensive disease in a great majority of the cases. The average period between registration and follow-up examination for the survivors was about 10 years.

In 1957, a new follow-up examination was made. We succeeded in obtaining information on all except 5 patients, 4 men and 1 woman. None of them had had

TABLE II

PATIENTS	NUMBER OF PATIENTS		
	MEN	WOMEN	TOTAL
Original series	111	179	290
Dead after 10 years (1950–51)	46 (41%)	52 (29%)	98 (33%)
Dead after 16 years (1957)	64 (58%)	76 (42%)	140 (48%)
Living after 16 years	43	102	145
Unidentified	4	1	5

TABLE III. OBSERVATION TIME*

PATIENTS	TOTAL		DEAD		LIVING		UNKNOWN	
	NUMBER	YEARS OBSERVED	NUMBER	YEARS OBSERVED	NUMBER	YEARS OBSERVED	NUMBER	YEARS OBSERVED
Men	111	1,083	64	414	43	648	4	21
Women	179	2,288	76	589	102	1,690	1	9
Total	290	3,371	140	1,003	145	2,338	5	30

*The observation time is measured to the nearest whole year.

definitive drug treatment before the last year. Sympathectomy had been performed in 7 patients, all women. At the first examination, 17 cases of malignant hypertension were found. The last follow-up examination revealed no new cases.

The average period between registration and follow-up examination for those who survived was now about 16 years. Now it was found that 76 women (42 per cent) and 64 men (58 per cent) had expired, i.e., 140 individuals (48 per cent). The average period between registration and death was about 6.5 years for men and 7.7 years for women. The total material observed represents 3,371 observation years, of which 2,288 observation years were for women (Table III).

Causes of Death.—Unlike other investigators, we found, in 1951, that the most common cause of death was cerebrovascular complications. The last follow-up, in 1957, confirms this observation (Table IV and Fig. 1). We found that of the dead, 55 per cent (50 per cent men and 59 per cent women) succumbed from a cerebral cause, 24 per cent (27 per cent men and 22 per cent women) from cardiac cause, 12 per cent (16 per cent men and 7 per cent women) from renal cause, and 9 per cent (7 per cent men and 12 per cent women) from miscellaneous causes.

Only 6 women (8 per cent) and 6 men (9 per cent) succumbed from a coronary condition or infarction. Eleven women (14 per cent) and 11 men (18 per cent) died from myocardial degeneration. The causes of death were found to be of about the same percentage in the first and second periods of observation.

TABLE IV. CAUSES OF DEATH*

PATIENTS	TOTAL	DEAD	CAUSES OF DEATH			
			CARDIAC	RENAL	CEREBRO-VASCULAR	MISCEL-LANEOUS
Men	111	64 (100%)	17 (27%)	10 (16%)	32 (50%)	5 (7%)
Women	179	76 (100%)	17 (22%)	5 (7%)	45 (59%)	9 (12%)
Total	290	140 (100%)	34 (24%)	15 (12%)	77 (55%)	14 (9%)
290 (100%)		48.2%	11.7%	5.1%	26.6%	4.8%

*The relative frequency of cerebrovascular death is higher in this material than that reported in most of the earlier publications.

TABLE V. NUMBER OF DEATHS ACCORDING TO "LABILITY" OF DIASTOLIC BLOOD PRESSURE

	LOWEST DIASTOLIC B.P. BELOW 95 MM. Hg	LOWEST DIASTOLIC B.P. LIKE OR ABOVE 95 MM. Hg
Men (number of patients)	43	64
Dead	12 (28%)	48 (75%)
Women (number of patients)	54	123
Dead	7 (13%)	67 (54.5%)
Total number of patients	97	187
Dead	19 (20%)	115 (62%)

Blood Pressure.—Figs. 2 and 3 give an impression of the case material in relation to lowest systolic and diastolic blood pressure readings at registration. A higher diastolic blood pressure is found in women, but the prognosis is better for women than for men.

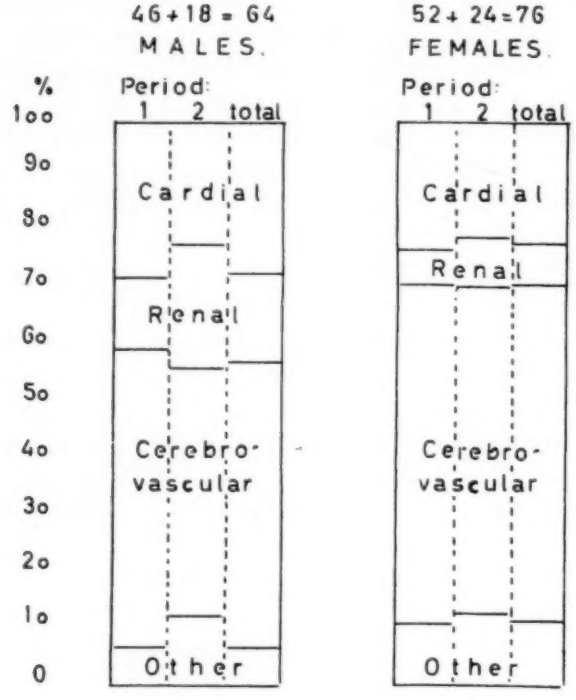


Fig. 1.—Causes of death.

The "lability" of the diastolic blood pressure at the time of registration proved to be a good indicator of the prognosis. Individuals whose diastolic blood pressure had a tendency to fall below 95 mm. Hg while they were resting, staying in bed, and/or taking sedatives, had a better prognosis. This was found in 97 patients (54 women and 43 men), of whom only 4 women (7 per cent) and 4 men (9 per cent) had succumbed in 1951. In 1957, it was found that of the total, 7 women (13 per cent) and 12 men (28 per cent) in this group had died (Table V).

In contrast, a "stable" diastolic blood pressure which never fell below 95 mm. Hg was found in 64 men and 123 women. In this group, 48 men (75 per cent) and 67 women (54 per cent) died during the observation period.

Death Rate.—The death rate has been determined on the basis of the number of dead per 1,000 years of observation. In 1951, for the entire group of patients the death rate for women was found to be 33.2 per 1,000 years of observation, i.e., more than seven times that of the general population with the same age distribution. For men the entire death rate, in 1951, was found to be 61.5 per 1,000 years of observation, or more than eleven times that of the general population. However, in the same year, individuals having a "labile" hypertension,

with a diastolic blood pressure which fell to values below 95 mm. Hg, had a death rate of 7.7 per 1,000 years of observation for women, and 10.7 for men, i.e., of about the same order as for the general population (Fig. 4).

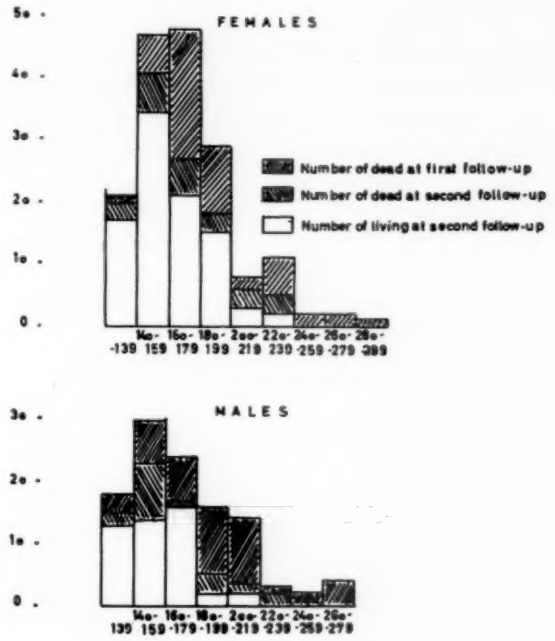


Fig. 2.—Number of patients according to lowest systolic blood pressure reading at registration.

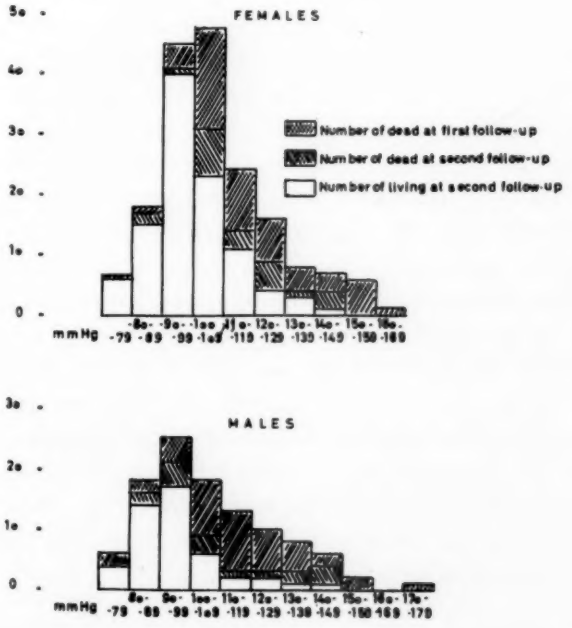


Fig. 3.—Number of patients according to lowest diastolic blood pressure reading at registration.

It is quite interesting that at the new follow-up in 1957, the death rate for women with "labile" diastolic hypertension was only 8.3 per 1,000 years of observation, i.e., about the same as that found 7 years before. For men the death rate was found to be 20.3 per 1,000 years of observation, i.e., not much higher than it had been 7 years before.

The patients with a diastolic blood pressure that never fell below 95 mm. Hg had a death rate of 47.3 for women and 99.8 for men per 1,000 years of observation in 1957, i.e., about five times that of men and women with a lower blood pressure at the time of registration.

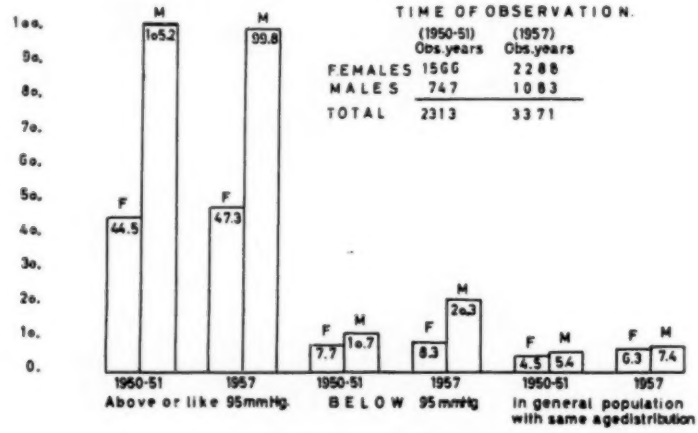


Fig. 4.—Death rate. Number of dead per 1,000 years of observation, in relation to lowest diastolic blood pressure reading on first examination.

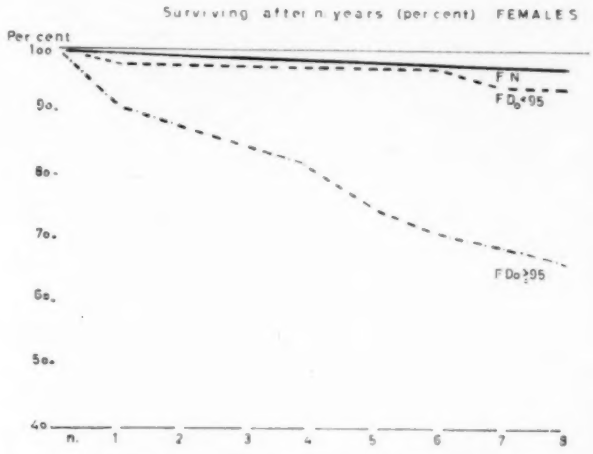
Survival Rate.—The survival rate will naturally show the same findings as the death rate. Figs. 5 and 6 show the survival rates for men and women with "labile" diastolic hypertension, in whom the blood pressure fell below 95 mm. Hg, and for those with "stable" diastolic hypertension, in whom the blood pressure never fell below 95 mm. Hg, with bed rest. For women the survival rate is better than for men with the same diastolic blood pressure. Individuals with "labile" diastolic hypertension are found to have a survival rate of the same order as for the general population with the same age distribution.

Other Symptoms and Signs.—Other symptoms and signs were also studied. Pathologic electrocardiograms and radiologic heart enlargement in this material were also found to be more frequent at registration in those who later died.

We have found in our material, as did Wagener and Keith[13] in theirs, a higher mortality in cases with retinopathy of the Wagener-Keith Grades 3 and 4. However, it has not been possible from one single symptom or sign to make valid conclusions for the prognosis. It seems to be of greater prognostic value to have a comparison of groups of symptoms and signs. We thus found that we derived considerable benefit from grouping symptoms and signs according to the classification of Hammarström and Bechgaard.[14]

Hammarström and Bechgaard Groups.—In 1950, Hammarström and Bechgaard divided hypertensives into the following groups: *Group I:* Patients with uncomplicated hypertension;

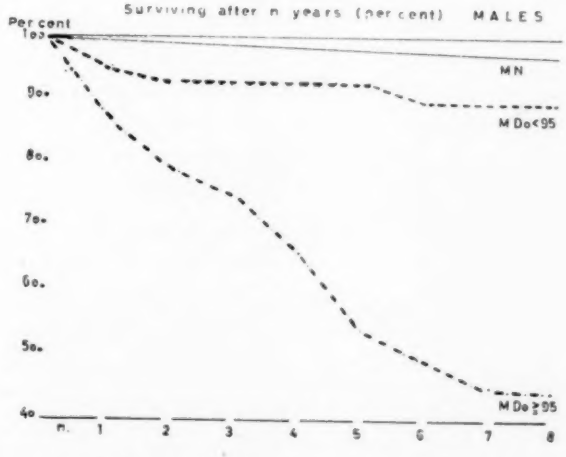
no marked symptoms and no signs, except elevation of blood pressure. *Group II:* Patients with diastolic blood pressure of at least 110 mm. Hg and marked symptoms, such as headache, dizziness, and fatigue, but without obvious signs of cardio-renal-vascular damage. *Group III:* Patients with signs of cardio-renal-vascular damage. *Group IV:* Patients with malignant hypertension evidenced by definite retinal exudates and/or papillary protrusion with or without retinal hemorrhages and a progressive course of the hypertensive disease.



FN: Normal population with same age distribution
FDo<95: Lowest diastolic blood pressure at registration below 95 mm Hg
FDo≥95: Lowest diastolic blood pressure at registration above or like 95 mm Hg

	FDo<95	FDo≥95
Size of material	54	122
Average age at registration	36.7 years	38.7 years

Fig. 5.—Survival rate in relation to diastolic blood pressure. Women.



MN: Normal population with same age distribution
MDo<95: Lowest diastolic blood pressure at registration below 95 mm Hg
MDo≥95: Lowest diastolic blood pressure at registration above or like 95 mm Hg

	$MD_o<95$	$MD_o\geq95$
Size of material	40	63
Average age at registration	33.5 years	39.3 years

Fig. 6.—Survival rate in relation to diastolic blood pressure. Men.

Having divided our case material according to the Hammarström and Bechgaard groupings of signs and symptoms, we found on the first examination that the survival rate for those in Groups I and II was about the same as for the general population. However, in Groups III and IV there was a lower survival rate, particularly in men. The last follow-up, in 1957, showed the same tendency (Figs. 7 and 8). Especially in the first 6 years of observation the survival rate for Groups I and II was about the same as for the general population. Women belonging to Groups III and IV showed a higher survival rate than did men in the same groups. None of the men and only 2 of the women belonging to Group IV were still alive; these 2 were invalids at the time of the second follow-up.

TABLE VI. WORKING CAPACITY OF PATIENTS AT SECOND FOLLOW-UP (1957)

PATIENTS	TOTAL	DEAD	WORKING FULL TIME	WORKING PART TIME	UNFITTED FOR WORK	WORKING CAPACITY UNKNOWN	UNKNOWN
Men	111	64	31	6	2	5	3
Women	179	76	30	54	5	13	1
Total	290	140	61	60	7	18	4

Working Capacity.—It is striking that the surviving hypertensive patients are, for the most part, working, but a large number, especially housewives, have reduced ability to work because of their high blood pressure (Table VI). Only 5 women and 2 men were found completely unable to work at the follow-up investigation in 1957.

DISCUSSION

Arterial hypertension is not a disease, but a symptom. In this investigation, all proved cases of secondary hypertension, as well as all cases with complications which could be thought to influence the prognosis, have been excluded.

Whenever earlier prognostic investigations of hypertensive patients have often shown diverging results, this may have been due to the original material being heterogeneous, with a varying number of cases of secondary hypertension. Also, the earlier material consisted mostly of older individuals.

In the present material, the mean age is lower than in most other surveys. The range in age difference is also small because only individuals under 46 years have been recorded, thereby preventing, to a certain degree, the chance of including patients who have been hypertensive for a longer time, as well as partly eliminating the factor of natural increase in blood pressure with increasing age.

In isolated observations[15] as in larger materials[16] it has been shown that patients can live for a long time with considerably increased blood pressure. However, investigations have shown that high blood pressure commonly has a serious prognosis.[1]

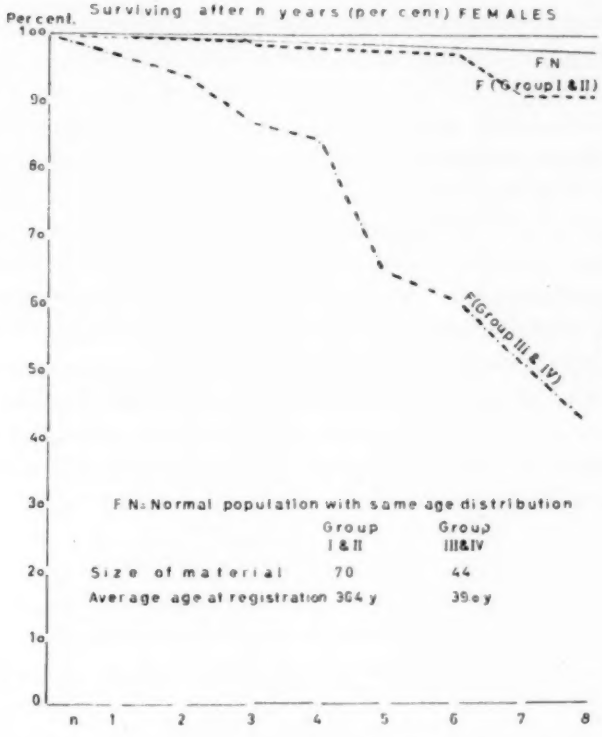


Fig. 7.

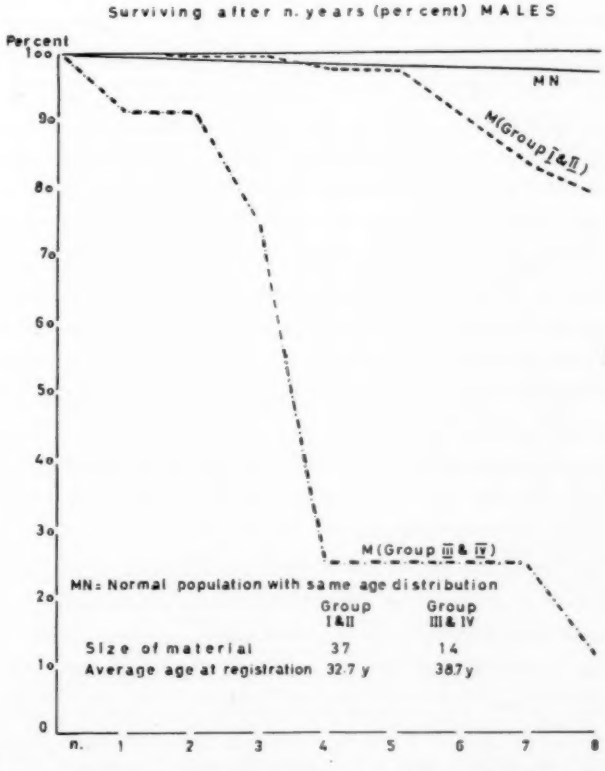


Fig. 8.

Fig. 7.—Survival rate in women classified according to the Hammarström-Bechgaard groups.
Fig. 8.—Survival rate in men classified according to the Hammarström-Bechgaard groups.

In our material it was found that a high systolic blood pressure over 200 mm. Hg was more frequent in those individuals who later died than in those who survived.

It is well known that the mortality in essential hypertension is greater in men than in women. In this material 58 per cent of the men and 42 per cent of the women died. The difference is so great that one must reckon that the female organism is better able to withstand high blood pressure than is the male.

Levy and associates[17] divided their material as follows: (1) patients with sustained hypertension with relatively fixed increased blood pressure, not falling below a value of 160 mm. Hg systolic and not below 100 mm. Hg diastolic; and (2) patients with transient hypertension in whom bed rest produced a fall in blood pressure below the mentioned values. Because this classification depends, to some extent, on estimation, we have tried to characterize blood-pressure types more exactly, and thus have chosen as a basic character the diastolic pressure. We have classified the blood-pressure types into "labile" and "stable" diastolic pressure.

"Labile" diastolic hypertension was diastolic blood pressure which fell to values below 95 mm. Hg after bed rest and sedatives. Such "labile" diastolic blood pressure was found at registration in 97 individuals, of whom 28 per cent of the men and 13 per cent of the women died during the observation period. In the group having "stable" diastolic hypertension, in which such a fall was not found, there was a mortality of 54 per cent in women and 75 per cent in men during the period of observation.

Investigations of mortality with methods used for life-insurance investigations give a good idea of the prognosis. Comparison with the population mortality table gives one a fair impression of the death rate when one considers the age range. The death rate for individuals belonging to the group with "labile" blood pressure was only 8.3 for women and 20.3 for men per 1,000 observation years. This is almost the same as for the total population in the corresponding age group. On the contrary, individuals with "stable" diastolic blood pressure showed a death rate of 47.3 per 1,000 observation years for women, and 99.3 per 1,000 observation years for men, that is, about five times the normal death rate both for men and for women.

In this material it is shown that individuals with changes corresponding to Hammarström and Bechgaard's Groups I and II had almost the same expectation of life as had the general population. But individuals in Group III showed a low survival rate, especially the men, and in Group IV all the men and all of the women except 2 died.

The causes of death in essential hypertension are cerebral, cardiac, or renal. Often several of the systems are affected at the same time. The renal death rate is higher in the earlier investigations, but in the more recent and larger investigations the proportion of renal deaths is about 10 per cent. In our material the renal death at follow-up investigation was found to be 9 per cent in 1950-51, and 12 per cent in 1957; these findings we take as evidence that the material did not contain many cases of primary renal disease, and that the worse prognosis in men is sometimes due to renal complications.

Death caused by cerebral diseases varied from about 20 to 45 per cent in the different materials. In the present investigation a higher frequency of cerebral deaths is found, namely, 55 per cent. This may be due partly to the fact that all patients who died with cerebral complications have been recorded as cerebral deaths, although there were symptoms of heart failure or renal complications at the same time. One has found this correct because the cerebral complications have been the direct cause of death in these cases.

Another reason for the high number of cerebral deaths is probably the age range, because the material, as mentioned, consisted of younger individuals, under the age of 46 at registration, who about 16 years later will still not have reached the age group in which heart failure symptoms are usual. Griep and associates,[12] who registered their patients at the relatively low age of 53 years, also found cerebral deaths in over 40 per cent.

Cardiac conditions, partly heart failure and partly coronary diseases, have been the dominating cause of death in the earlier investigations. Cardiac cause of death is found in only 24 per cent of our material. The majority of such deaths were cases of heart failure, while coronary artery disease rarely was found to be the cause of death. Only 6 women (8 per cent) and 6 men (9 per cent) died of myocardial infarction. There is a striking resemblance between the percentage distribution of causes of death recorded in the two follow-up investigations, in 1950-51 and in 1957.

At the last follow-up in 1957, we found few patients who were quite unable to work. Patients working part time were frequently found among housewives, but approximately one half of the patients living tried to fill a full-time job.

SUMMARY

1. In 1944, a registration of hypertensive patients from several departments of internal medicine in Oslo was undertaken. The patients, who were all less than 46 years of age at the time of registration, had been hospitalized for different ailments. All of them had a systolic blood pressure of 160 mm. Hg or more, or a diastolic blood pressure of 95 mm. Hg or more. This primary material consisted of 290 patients, 179 women (62 per cent) and 111 men (38 per cent). Cases of secondary hypertension were excluded, as well as cases with complications which might possibly influence the prognosis. The patients have been re-examined several times, the last time in 1957, with regard to the prognosis. During the observation period, on an average of 16 years, none of the patients received special antihypertensive treatment.

2. The prognosis was found to be much better in patients with a labile diastolic hypertension, i.e., patients whose diastolic blood pressure went below 95 mm. Hg during bed rest and treatment with sedatives, than in patients with a more stabilized diastolic hypertension. Only 7 (13 per cent) of 54 women and 12 (28 per cent) of 43 men with labile diastolic hypertension died during the observation time. On the other hand, 64 (54 per cent) of 123 women and 48 (75 per cent) of 64 men with more stabilized diastolic hypertension died.

3. The death rate, i.e., number of dead per 1,000 years of observation, was found to be 8.3 for women and 20.3 for men with labile diastolic hypertension.

These were approximately the same death rates as for the general population in Norway, the age distribution being taken into consideration. Among patients with the more stabilized diastolic hypertension, the death rate was 47.3 for women and 99.8 for men. This means that it is about five times higher than in the groups with a labile hypertension.

4. The causes of death in the total material are grouped as follows: cerebrovascular (55 per cent), cardiac (24 per cent), renal (12 per cent), and other causes (9 per cent). Cerebrovascular causes of death were found frequently and fairly constantly during the periods of observation before and after 1950-51. The cardiac deaths were most frequently caused by myocardial degeneration. In all, 11 women (14 per cent) and 11 men (18 per cent) died from myocardial degeneration without coronary disease, whereas only 6 women (8 per cent) and 6 men (9 per cent) died of myocardial infarction.

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Focal Application of Hypertonic Solutions of Sodium Chloride on Impulse Formation in the Heart of the Dog

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Focal application of a hypertonic solution of sodium chloride to the atria or ventricles of the exposed heart of the dog leads to the appearance of coupled extrasystoles or short bouts of ectopic paroxysmal tachycardia.[5] When 0.05 c.c. of a 20 per cent solution of sodium chloride is injected into the taenia terminalis, in which the sinus node is situated, and one of the vagus nerves is stimulated in the neck with a faradic current, atrial flutter, atrial fibrillation, or a paroxysmal atrial tachycardia appears.[11] These effects are fleeting, and are observed for 4 to 5 minutes immediately following the injection.

This investigation was continued and the effect of injections of the hypertonic solution in two other areas was studied: these areas were the atrioventricular node and the appendix of the left atrium, which is supposedly devoid of specialized automatic fibers.

METHOD

As in the previous experiments mongrel dogs were anesthetized with Nembutal (10 to 12 mg. per Kg.) and morphine (15 mg. per Kg.). The heart was exposed by removing the sternum and opening the pericardium. A shielded electrode was applied to the right vagus nerve in the neck; the vagus nerves were not severed. Stimulation of the vagus was performed with a Cambridge inductorium. The injections of the solution of 20 per cent sodium chloride were performed with a tuberculin syringe. The electrocardiogram was registered in Lead II.

RESULTS

Injection Into the Area of the A-V Node.—Because of experimental difficulties with the heart in situ and unopened, not all injections reached the desired area. They were attempted either through the wall of the right atrium in the direction of the atrial septum near the A-V border, or the heart was lifted from the pericardial bed and the injection was performed as nearly as possible in front of the inflow area of the coronary sinus vein into the right atrium. The latter method was more reliable.

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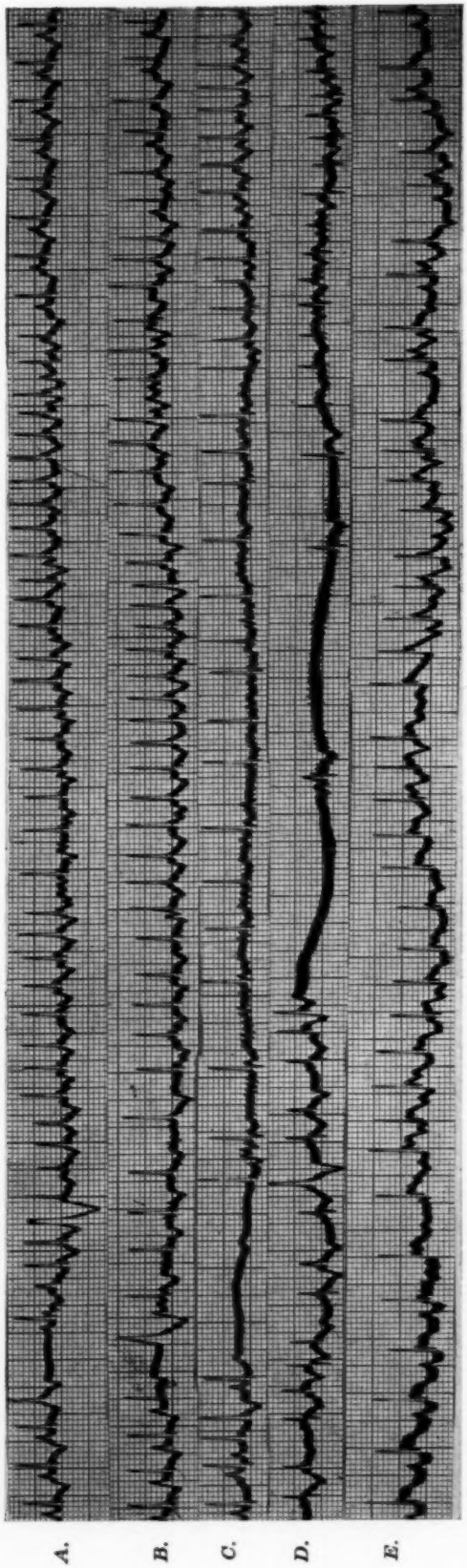

Fig. 1.—*A*, *B*, and *C* were obtained in the experiment of May 13. The solution of sodium chloride had been applied to the left atrial appendix (*A*). The tracing shows three sinus beats followed by an atrial extrasystole. Vagus stimulation leads to the immediate appearance of a short attack of atrial fibrillation. Application of the solution of sodium chloride to the area of the A-V node through the wall of the right atrium (*B*) leads to the appearance of atrial fibrillation as soon as the vagus is stimulated. The first P wave of the fibrillation is negative and visible in the T of an ectopic ventricular beat. Two atrial extrasystoles are seen after the fibrillation subsided; 5 minutes later the solution of sodium chloride was injected into the area of the inflow of the coronary sinus vein from the back of the heart. Atrial extrasystoles appeared (*C*) with positive P waves, and atrial fibrillation set in shortly after the beginning of the vagus stimulation. Vagus stimulation alone before the injection of sodium chloride and after the effect of each injection had subsided did not cause atrial extrasystole nor fibrillation. *D* was obtained in the experiment of April 19. Following the injection of sodium chloride from the back of the heart into the A-V node area, atrial extrasystoles appear with deeply negative P waves; vagus stimulation leads to atrial fibrillation with negativity of the first P wave. *E* was obtained on June 3. This time the injection into the area of the A-V node from the back of the heart caused injury to ventricular muscle fibers and a displacement of the RS-T segment. During a short vagus stimulation, the end of which is seen with the disappearance of a slight distortion of the tracing, atrial fibrillation appeared. An atrial bigeminal rhythm prevailed for a short time after the fibrillation ended, with the extrasystoles having positive P waves.

Fig. 2.—In the experiment of May 20, injection of the solution of sodium chloride into the area of the A-V node from the back caused complete A-V block. Vagus stimulation inhibited the atria, as seen in both *A* and *B*. After the vagus stimulation was stopped, the P waves show the diphasic picture characteristic for a vagus effect and caused by a shortening of the action potential and a deepening and shortening of the T_a wave. A short attack of atrial flutter with inverted P waves followed. Repeated vagus stimulation following this caused three bouts of atrial fibrillation.

Atrial extrasystoles appeared in 7 experiments following the injection, just as with an injection into the area of the sinus node (Fig. 1). Atrial fibrillation or flutter was seen following vagus stimulation in 12 of 17 experiments (Fig. 1,*B*). In 2 experiments A-V block appeared for 10 and 14 minutes, respectively, following the injection (Fig. 2), demonstrating that the A-V conduction system had been reached by the injection. In most instances a displacement of the RS-T segment also appeared (Fig. 1,*D* and *E*) because of injury to the ventricular myocardium at the A-V border.

Inverted P waves were seen in isolated extrasystoles, in flutter (Figs. 1,*D* and 2), and in the first few F waves of fibrillation in 4 experiments, but in the others the P waves were low positive.

The flutter or fibrillation was of short duration, lasting from a few seconds up to 94 seconds. The arrhythmias appeared either immediately upon vagus stimulation (Fig. 1,*A-C*) or after prolonged stimulation (Fig. 2). The result was reproducible for 2 to 4 minutes, and then a new injection was necessary. In 3 experiments A-V nodal tachycardias appeared which were not stopped by vagus stimulation.

Injection Into the Outer Wall of the Appendix of the Left Atrium.—The application of the solution in this instance is difficult because of the thinness of the wall. An attempt was made to inject into one of the thin muscle bundles of the appendix, but some spilling of the solution into the cavity of the left appendix could not be avoided. While vagus stimulation before the injection never led to atrial fibrillation, the injection alone caused atrial fibrillation in 7 out of 17 experiments; after the injection, vagus stimulation provoked flutter or fibrillation 15 times, and did so repeatedly in 14 experiments. The focal origin of these attacks of fibrillation is proved by the fact that they could invariably be stopped at once by cooling the area on which the sodium chloride was applied. The P waves of the extrasystoles appearing before or after the stimulation of the vagus were always positive.

DISCUSSION

These experiments show that application of a strong hypertonic solution in the A-V node area and into the left atrial appendix, combined with vagus stimulation, causes atrial flutter or fibrillation in the majority of the experiments. Since there are, in all probability, no specialized fibers in the appendix of the left atrium, we may assume that the combined effect of a hypertonic solution of sodium chloride and acetylcholine leads to fibrillation originating in the common myocardial fiber. Certainly this will also be true for most of the instances of flutter after the injection into the area of the A-V node, since with the technique used, injection of sodium chloride into the A-V node tissue could only be certain in those experiments in which A-V block appeared and the P waves showed the typical inversion in Leads II and III for this focus of origin.[7] That A-V node extrasystoles in the dog may show positive P waves in Lead II can be deduced from previous experiments,[12] but is not established beyond doubt.

The focal origin of flutter in the A-V node has been proved; topical application of acetylcholine to the atria of the dog after clamping of the sinus node causes fibrillation, which disappears when the A-V node is cooled, and which reappears when the cooling is discontinued.[9]

Application of a hypertonic solution of sodium chloride as used in the present experiments causes a marked osmotic effect and a change of pH which cannot be neglected. However, a specific effect of the sodium ions seems to be responsible, for the following reasons. We never succeeded in initiating extrasystoles or fibrillation by focal application of dilute acids and numerous other substances with strong physical effects but with no known action on impulse formation in the heart. On the other hand, various substances which are known to cause ectopic impulses in the heart do so when applied focally, even in a great variety of concentrations and in the characteristic manner typical for each one.[10] Thus, sodium chloride always causes ventricular extrasystoles with fixed coupling or a regular tachycardia, while barium chloride produces irregularly coupled extrasystoles and irregular tachycardias in the same way as after intravenous injection. Aconitine leads to the characteristic regularly rapid impulse formation described in detail elsewhere.[8] Veratrine causes only parasystolic ectopic rhythms, with protection of the ectopic pacemaker from the prevailing sinus rhythm. Digitalis focally applied causes regular extrasystoles after a prolonged latent period, and strophanthin causes the same extrasystoles but after a much shorter latent period.[6] Therefore, we believe that it is not the hypertonicity but the surplus of sodium ions which is responsible for our results. In investigations on the effect of hypertonic solutions of sodium on the Ranvier node of the frog nerves it was found that the action current is prolonged to a remarkable degree so that a veratrine effect was imitated. Under the influence of a 5 per cent solution of sodium chloride a nerve fiber fires a series of impulses following application of a single induction shock.[13]

The rapid disappearance of the effect of the solution of sodium chloride is presumably due to the quick absorption of the solution.

It may be speculated that a surplus of sodium ions which enhances the slow depolarization of the pacemaker fibers in diastole[2] leads also to a slow depolarization of common myocardial fibers, particularly when acetylcholine is set free. It is proved that the latter substance enhances the entry of sodium into the cells.[1,3,4]

CONCLUSIONS

Injection of a 20 per cent solution of sodium chloride into the area of the A-V node of the dog will occasionally cause A-V block or A-V tachycardia, but more often it will produce paroxysmal atrial flutter or fibrillation. This is particularly so during faradic stimulation of the right vagus nerve in the neck. These latter arrhythmias (atrial flutter or fibrillation) are also noted during vagal stimulation when the injection is given in the outer wall of the appendix of the left atrium. The implications of these findings are discussed.

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A Simple Device for Measuring Time Intervals in the Electrocardiogram and for Determining the Electrical Axis of the QRS Complex

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In analyzing an electrocardiogram it is necessary in some cases to determine exactly the time intervals between different points of the curve. The size of these critical intervals, i.e., the P-Q interval, length of the QRS complex, or Q-T interval, is mentioned in the handbooks on this subject in terms of 1/100 second. However, it is rather difficult to measure these distances to a tolerance of 1/100 second on an electrocardiogram, registered with the standard velocity of 2.5 cm. per second, where 1 mm. conforms to 0.04 second. Even with the help of a magnifying glass, the determination of the beginning of a P wave, or the estimation of the length of a Q-T interval, is merely a matter of guessing fractions of millimeters and then multiplying by 0.04 in order to obtain the value in 1/100 second.

For this reason, a measuring wedge is engraved on the backside of a clear glass Perspex ruler (Fig. 1). Applying this ruler on the cardiogram, the divisions are in direct contact with the lines on the paper, thus enabling parallax-free, exact measuring of the intervals. The advantage of a transparent ruler above a ruler of opaque material is that in laying it on the paper the curve as a whole remains visible, facilitating the orientation. The left side of the wedge is divided into 2/100 second, agreeing with the distance between the legs of the angle. To measure the intervals accurately, it is necessary to keep the bisectrix of the angle parallel to the vertical lines on the paper. Examples for determining the Q-S, P-Q, and Q-T intervals are given in Fig. 1,*B*, *C*, and *D*.

To determine the heart rate, the right side of the wedge is divided into strokes per minute. Placing the legs of the angle on two subsequent R or S waves, one can read the heart rate at this point (Fig. 1,*A*).

For determining the algebraic sum of the QRS complex, the ruler is placed with the bisectrix parallel to the horizontal lines of the paper. The distance of the bisectrix to the isoelectric line times 2 indicates this algebraic sum: positive, if it is above, and negative, if it is beneath the isoelectric line (Fig. 1,*E*).

Construction of the electrical axis is done in the usual way for Lead I and Lead III. Engraved on the same ruler are two scales, perpendicular to each other. The vertical scale is for Lead I (negative above and positive below), and the single horizontal scale is for Lead III (Fig. 2). A divided disc slides

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over the top of these scales, moving its center along the horizontal Lead III scale. Moreover, the disc can be turned. To find the electrical axis, place the center of the disc on the value found for the algebraic sum in Lead III on the corresponding scale. Then turn the disc, and let the pointer cross the vertical scale on the number found for Lead I (plus or minus). The electrical axis can now be read on the rim of the disc.

The example diagrammed in Fig. 2 shows the algebraic sum for Lead I as +20 units, and that for Lead III as −17 units. Put the center of the disc on 17 of the horizontal scale. Then set the pointer on figure 20 of the positive scale for Lead I. Read the electrical axis on the right side of the disc: −23°. If the value for Lead III was +17, read at the left side of the disc: +57°. The vector length is 26 units (to be read on the pointer from the center of the disc to its intersection with the vertical scale).

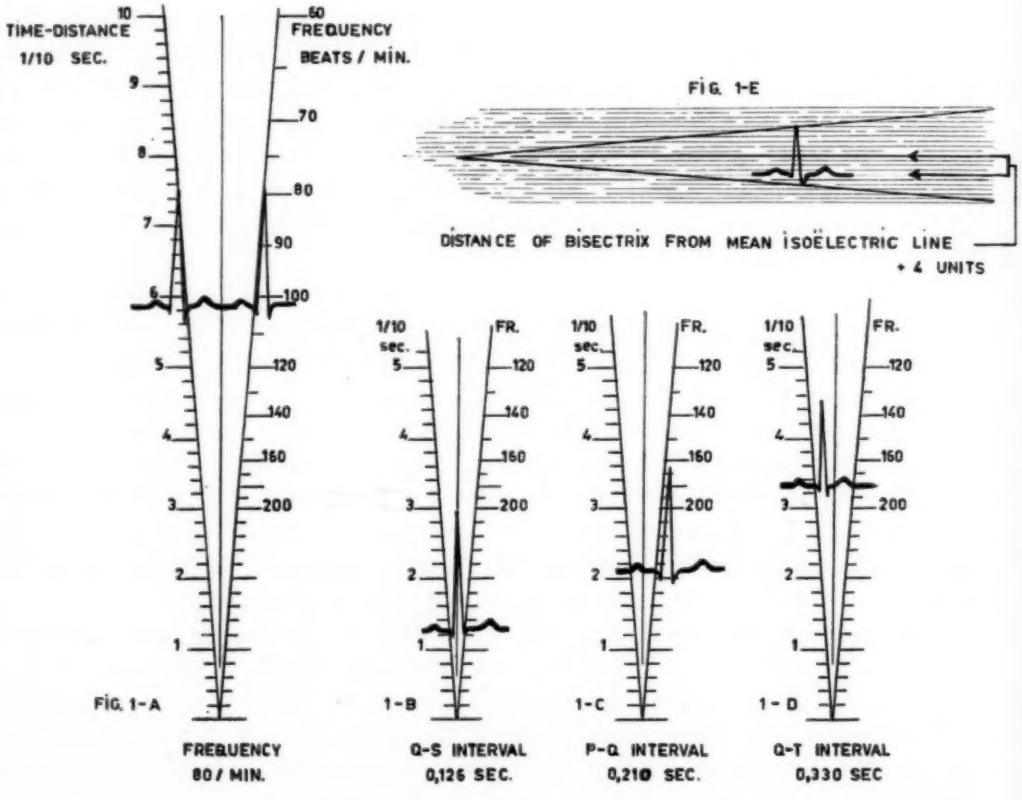

Fig. 1.—In this figure several possibilities are shown for using the ruler on the electrocardiogram. *A* shows the measuring wedge, placed on a schematically drawn ECG, in position to determine the heart rate. The two legs of the angle are laid on two subsequent R waves. (Of course, two subsequent Q or S waves would serve as well, if they were sufficiently clear.) The heart rate in this example is 80 beats per minute—indicated on the right side of the wedge. The time distance between two R waves at this frequency is 0.75 second—read on the left side of the scale. In *B*, *C*, and *D*, measurement of the most important intervals in the ECG is shown. Note that the minor divisions on the left side of the scale correspond to time intervals of 0.02 second. *E* shows the ruler in the horizontal position for determination of the algebraic sum of the R and the S amplitudes in Lead I. The upper leg of the angle is placed on the top of the R wave, and the lower leg on the S wave. The bisectrix is parallel to the horizontal lines on the paper. The distance between the bisectrix and the isoelectric line in this example is +4 units; therefore, the algebraic sum of the R and S amplitude is +8 units (see text).

The instrument described is simply a suggestion, which anyone can develop further to meet his own requirements for rapid and exact evaluation of a cardiogram. Using the device on a cardiogram of good quality, the accuracy is better than 1/100 second for the time intervals and saves much calculation in determining the electrical axis. The complete instrument measures 4 by 17 cm.

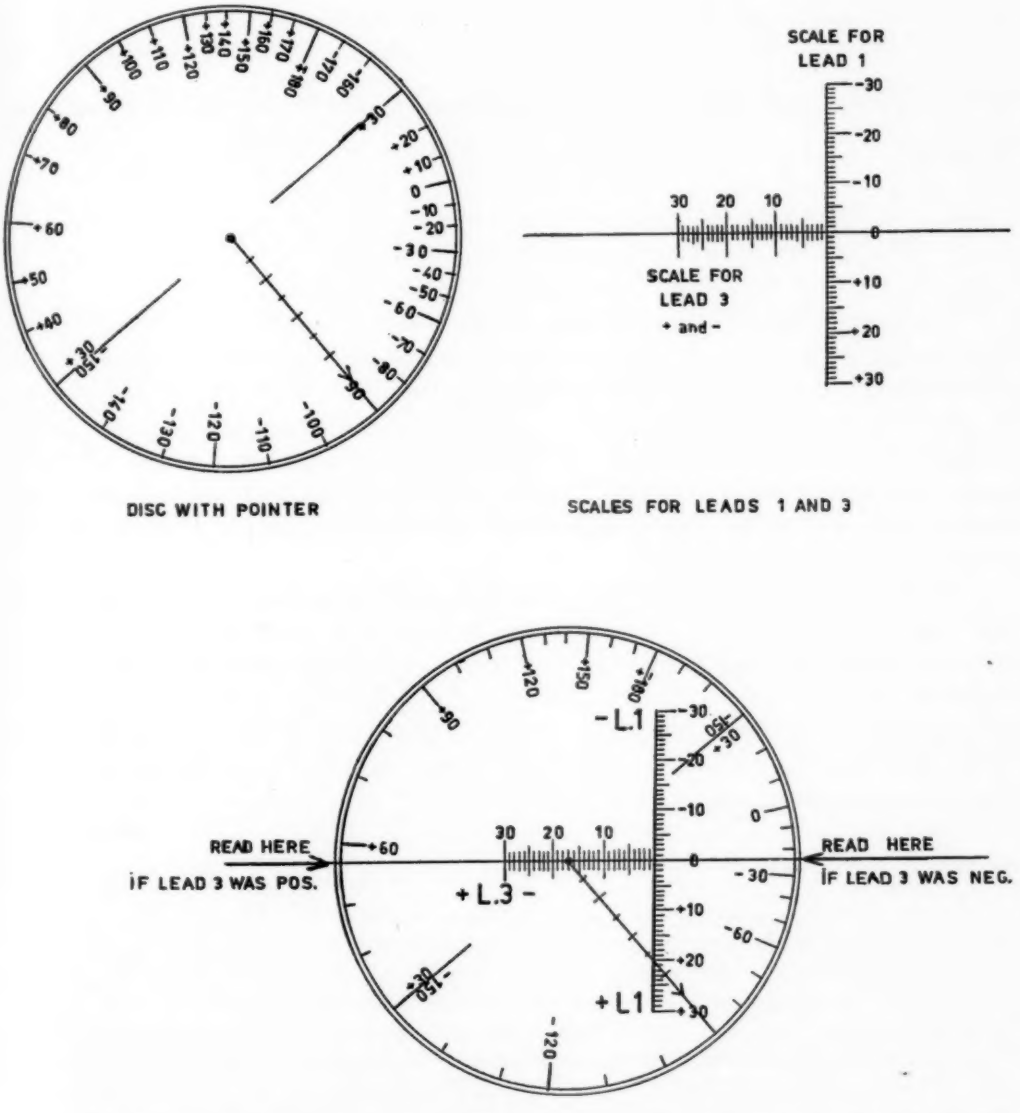

Fig. 2.—The rotating disc for determining the electrical axis is designed separately from the scales, in the upper part of this illustration. Note that for the values found for Lead I there are two scales, one for negative values and one for positive values. For the values found for Lead III a single scale is used (the horizontal one). This is done to limit the distance which the center of the disc has to be moved along the Lead III scale. Instead of two scales for Lead III the different angles of the electrical axis, in case of a positive or negative value of the algebraic sum in Lead III, can be read at two different points of the rim. For purposes of clarity, fewer numbers are used in the lower part of the illustration wherein the rotating disc is shown assembled with the scales in the position corresponding to the example described in the text.

Serum Cholesterol and Lipid Phosphorus in Dogs on an Atherogenic Regimen

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For many years efforts have been made to devise some means of recognizing those people who can be expected to develop clinically significant atherosclerosis. The frequent correlation of hypercholesterolemia with clinical manifestations of atherosclerosis has been pointed out by numerous investigators.[1-3] Other studies, however, have resulted in opposite conclusions,[4] and there has been much evidence presented to support the view that the cholesterol-phospholipid ratio is of more significance in this regard than is the absolute concentration of either of its components.[1,2,5,6]

This communication reports a study of the levels of serum cholesterol and lipid phosphorus and the ratios of cholesterol to lipid phosphorus in a group of dogs on an atherogenic regimen. The object was to determine which of these variables is most helpful in predicting the incidence of arterial lesions under the conditions of the experiment. The very wide range of concentrations of lipids that can be studied in this way might yield information not available from a comparable study in human beings.[7]

MATERIAL AND METHODS

Fifteen adult mongrel dogs, three males and twelve females, were studied during a 2½-year period for a total of 215 dog-months. They were maintained on an atherogenic regimen based on that first described by Steiner and Kendall.[8] Suppression of thyroid function was achieved by thiouracil, propylthiouracil, and/or radioiodine, and cholesterol (precipitated from an ether solution) was fed as 5 per cent of an ad libitum diet. Serum was obtained at intervals of 2 weeks. Total cholesterol was determined in most instances by the method of Hoffman,[9] and in some by that of Pearson and associates.[10] Youngburg and Youngburg's method[11] for lipid phosphorus was used during the first 2 years, and subsequently that described by Fister[12] was employed. Four hundred and sixty-two specimens of serum were analyzed.

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RESULTS

Fig. 1 shows that there is a high degree of positive correlation between the level of serum cholesterol and that of lipid phosphorus ($r = 0.9$, $p = < 0.001$). When two variables are related to each other in such a fashion, the ratio of one to the other bears a curvilinear relationship to each of its components (Fig. 2). The ratio of cholesterol to lipid phosphorus increases very little with large increments of cholesterol and lipid phosphorus above about 1,750 and 50 mg. per cent, respectively.

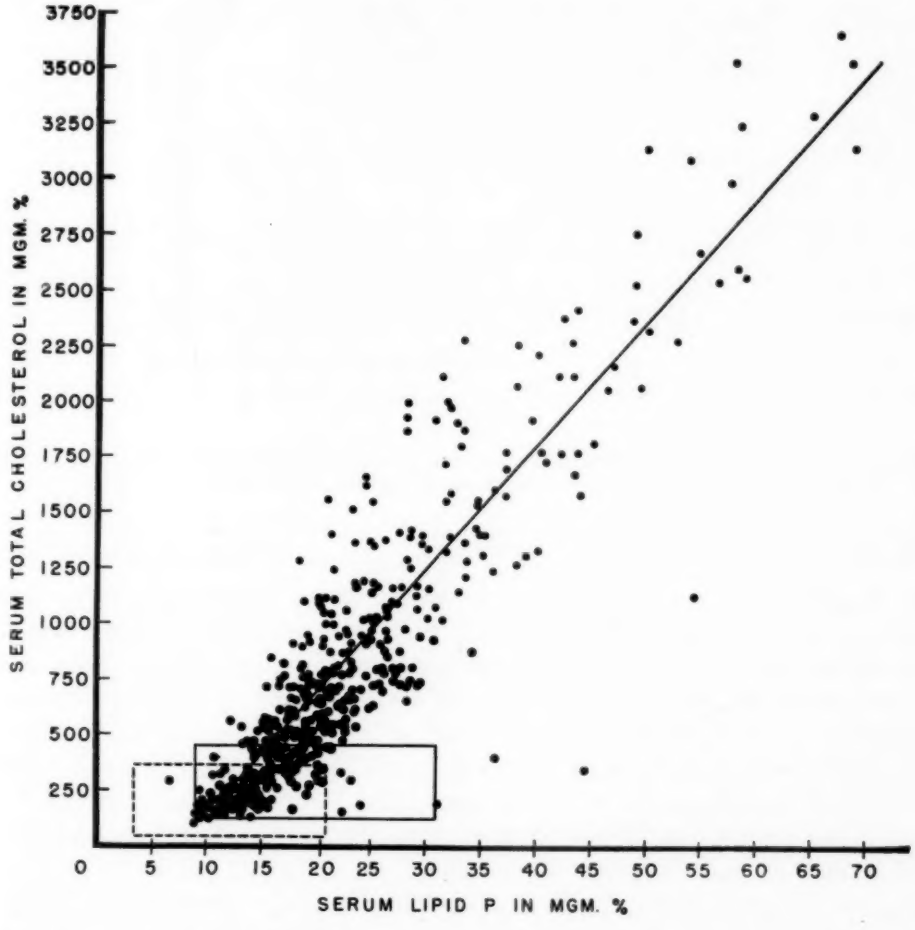

Fig. 1.—Relation of total serum cholesterol and lipid phosphorus in 462 specimens of serum obtained from fifteen dogs studied for a total of 215 dog-months ($r = 0.9$, $p = < 0.001$). The solid rectangle represents the range of normal values; dotted, mean ±2 standard deviations.

DISCUSSION

Bevans and associates[13] have shown that when dogs are subjected to an atherogenic regimen such as that described above, the incidence of arterial atheromata can be predicted on the basis of the concentration of serum cholesterol. Quantitative expression of the extent of atherosclerosis is difficult, but

in 6 years' experience with the experimental disease in dogs the authors have observed that the size and extent of the lesions may be expected to be proportional to the concentration of cholesterol in the serum, while their character, whether early and composed mostly of foam cells or older with scarring and calcification, is a function of the time during which the lipid metabolism has been disordered.

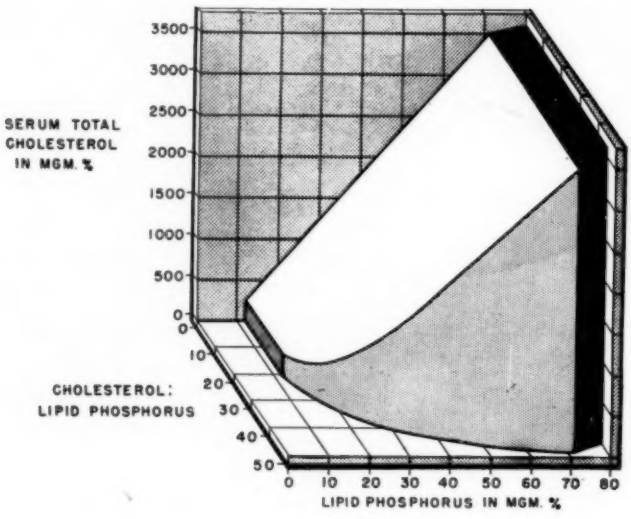

Fig. 2.—Schematic diagram of interrelations of serum lipids in dogs on an atherogenic regimen. The curves are based on the data presented in Fig. 1.

Since the level of serum lipid phosphorus varies *pari passu* with that of total cholesterol, it is apparent that an event which can be related to changes in one can be related with approximately the same degree of accuracy to changes in the other, and that knowledge of the absolute concentrations of both of them does not increase this accuracy. As the levels of serum cholesterol and lipid phosphorus increase above normal, there is at first a comparable rise in the ratio of cholesterol to lipid phosphorus. At higher concentrations, however, considerable increments of lipids are associated with very little increase in the ratio. This means that, as far as predicting the incidence and character of arterial lesions in these animals is concerned, elevation of the ratio is as useful a measure as is elevation of either of its components. If dependence is placed on the ratio alone, however, the size and extent of the lesions cannot be anticipated nearly so well, since marked elevation of its component lipids will be masked.

SUMMARY AND CONCLUSIONS

A study of total concentrations of serum cholesterol and lipid phosphorus and the ratio of cholesterol to lipid phosphorus in dogs on an atherogenic regimen has been described. The levels of cholesterol and lipid phosphorus have a high degree of positive correlation and are equally useful in predicting atherogenesis.

Above cholesterol levels of about 1,750 mg. per cent and lipid phosphorus levels of about 50 mg. per cent, the ratio of cholesterol to lipid phosphorus changes very little. This ratio, then, is a less sensitive indicator of atherogenesis in these dogs than is either of its components.

The help of Mrs. Con O. T. Ball in analysis of the data, and of Dr. G. G. Rudolph in determination of the serum lipids is gratefully acknowledged.

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Importance of the Unipolar Leads in the Diagnosis of Dextrocardias, Levocardias, Dextropositions, and Dextrorotations

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The electrocardiogram provides definite aid in the diagnosis of dextrocardias, dextrorotations, and dextropositions, either complicated or not by other congenital heart disease.

An electrocardiographic interpretation must necessarily be understood in all of its aspects before it can be considered as a complete study. "Deductive electrocardiography" would perhaps be the correct name for this type of electrocardiographic interpretation. The sequence of the activation of the heart which explains the electrocardiographic morphologies is indispensable to an understanding of the tracing.

Using the aforementioned method we are able to determine the position of the auricles and ventricles within the chest. In this paper we present several examples, one of which will serve to define clearly our point of view. An electrocardiogram was interpreted by us as indicating a transposition of the ventricles. Clinicians and radiologists refused to admit our diagnosis and demurred. We took the stand that unless there was ventricular transposition, we simply did not understand the tracing. The angiocardiographic study proved the transposition of the chambers.

MATERIAL

Thirty-five electrocardiograms corresponding to proved anomalies of position of the heart were studied. They were classified as follows:

I. *Dextrocardia* with situs inversus was observed in 25 cases. (A) Nine (36 per cent) were uncomplicated. (B) Sixteen (64 per cent) were complicated, having besides dextrocardia other cardiopathies distributed as follows: (1) nine congenital cases (36 per cent): 2 tetralogy of Fallot, 2 Eisenmenger complex, 1 transposition of the great vessels, 1 common trunk, 2 patent ductus arteriosus, and 1 interventricular septal defect; and (2) seven acquired cases (28 per cent): 3 chronic cor pulmonale, 2 coronary heart disease, 1 mitral disease (stenosis and mitral insufficiency), and 1 undiagnosed.

II. *Dextrorotation* without transposition of the cavities was observed in 6 cases. Five were complicated with the following cardiopathies: 2 tricuspid atresia, 1 tetralogy of Fallot, 1 trilogy of Fallot, 1 transposition of the great vessels. In one case the heart was normal.

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III. *Dextroposition* was observed in 3 cases. In 2 of these the displacement of the heart toward the right side was caused by a fibrous tuberculous process of the right lung, while in the third the displacement was due to a large left pleural effusion.

IV. *Levocardia* was observed in 1 case, that of a 4-year-old child. Cor triloculare monoventriculare with pulmonary stenosis was found in a heart anatomically situated to the left with visceral transposition.

RESULTS

I. DEXTROCARDIA WITH TRANSPOSITION OF THE CAVITIES AND SITUS INVERSUS

A. *Uncomplicated Cases.*—Uncomplicated cases of dextrocardia with situs inversus are recognized by the following electrocardiographic considerations:

1. *Negative P Wave in Leads I and aVL.*—This sign is of value when the P wave is negative in the major part of the left hemithorax and positive in the major part of the right hemithorax (thoracic circle) at the level of the apex of the heart. Such electrocardiographic findings suggest the existence of transposed auricular cavities, and is in accord with the mean general direction of atrial activation from left to right, contrary to that of normal activation from right to left. This happens because the superior vena cava as well as the sinus node are situated on the left side.

With the above electrocardiographic criterion we are able to establish the diagnosis of transposition of the auricles with or without ventricular transposition.

The positive P wave in Lead aVR has a significant diagnostic value in auricular transposition, although it is of lesser importance than in leads taken around the thorax (thoracic circle). This seems logical inasmuch as the P wave may be positive in the unipolar lead of the right arm in cases of dextrorotation.

In order for the diagnosis of dextrocardia to be made the electrocardiogram must show the characteristic electrocardiographic features of ventricular transposition which will be commented upon later.

Fig. 1 shows the electrocardiogram of a 24-year-old woman with dextrocardia, but no other cardiopathy. The alterations of the P wave are characteristic: negative P wave in Leads I and aVL; isoelectric or slightly negative P wave in Leads V_5 and V_6. By contrast, it is positive from Lead V_3R through Lead V_6R. The spatial axis of the P wave (SÂP) is directed from left to right, from posterior to anterior, and from upward to downward. These P-wave changes indicate that the stimulus originates on the left side, suggesting auricular transposition. This diagnosis is confirmed by the distribution of the ventricular potentials which will be discussed later.

Nodal rhythm is frequently observed in real dextrocardia with situs inversus. This rhythm is recognized in a heart without dextrocardia by a negative P wave in Leads II, III, and aVF and a positive P wave in Lead aVL. The mean electrical axis of P (ÂP) is found around $-60°$ and is spatially directed forward, upward, and to the left. It points anteriorly and superiorly because the A-V node is placed in the inferior and posterior portion of the interauricular septum. It points toward the left because the left auricular electrical forces predominate over the right auricular ones (Fig. 2).

If the magnitude of the electrical forces originating in both auricles were identical, then the mean spatial vector would point upward, anteriorly, and would be localized at the midline (ÂP $-90°$ in the frontal plane).

In a few cases of right auricular hypertrophy with nodal rhythm the electrical axis of P points from the back toward the front, upward and toward the right; this latter direction is caused by the increased electrical forces originating in the right auricular muscle (Fig. 3).

In cases of dextrocardia with nodal rhythm and without heart disease the mean spatial electrical axis of P has a superior, anterior, and rightward direction, because of auricular transposition. Normally, the electrical forces of the left auricle are larger than those of the right auricle (Fig. 4).

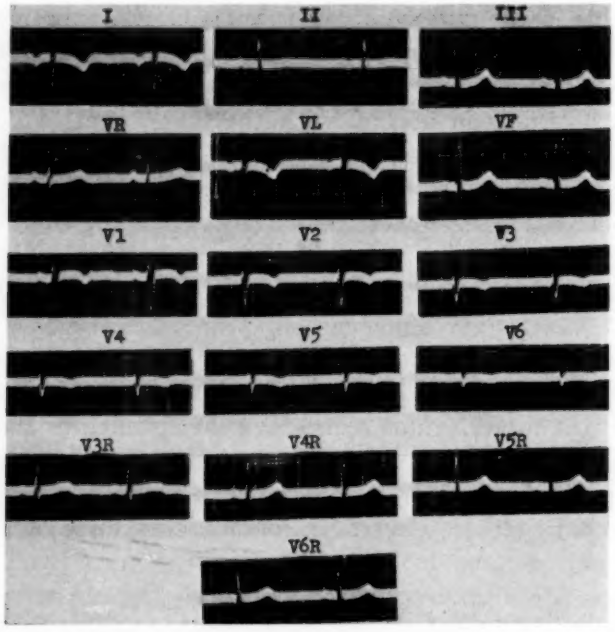


Fig. 1.—Tracing from a patient with dextrocardia, but no other cardiopathy. Note the T-wave changes.

Fig. 5 shows tracings in a typical case of real dextrocardia (with transposition of both auricles and ventricles). The P wave is negative in Leads I, II, III (nodal rhythm), V_3 and V_6 (left hemithorax), and positive in Lead aVR. The ÂP in the frontal plane is situated close to $-120°$, and is spatially directed anteriorly, superiorly, and to the right. There is a nodal rhythm, and the axis of the P wave points toward the right because of the right-sided left auricle. The wide P wave accounts for most of the P-R interval (0.15 second), and is suggestive of left auricular hypertrophy; this electrocardiographic diagnosis is supported by the clinical diagnosis of double mitral lesion.

There are many situations in which the differential diagnosis is difficult, as in the case illustrated in Fig. 6. The diagnosis of dextrocardia with nodal rhythm was suspected because of the presence of negative P waves in the standard leads and in Lead aVF. A chest x-ray showed a right-sided heart.

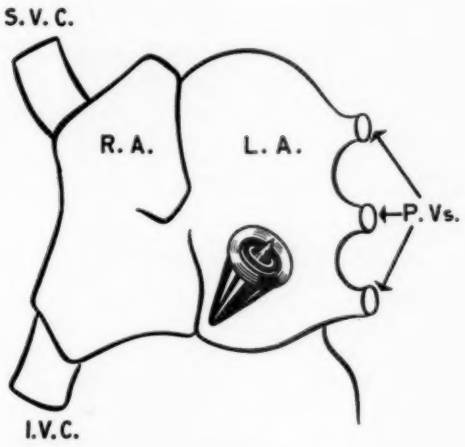
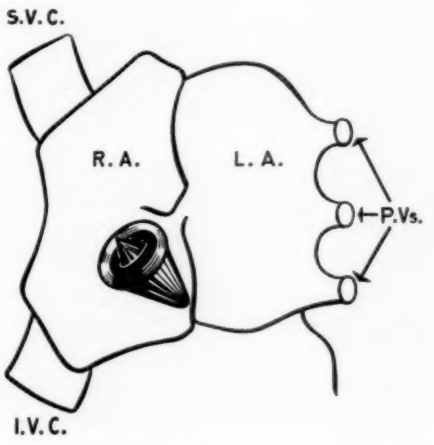


Fig. 2.



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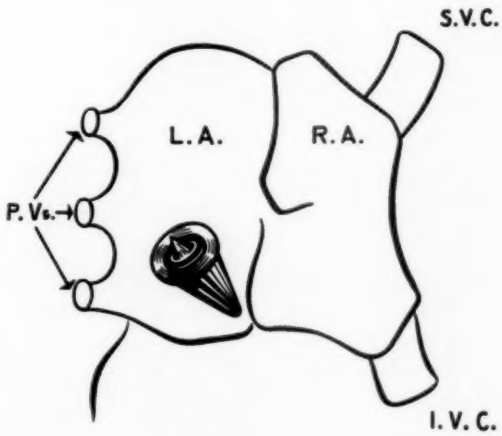

Fig. 4.

Fig. 2.—The mean electrical axis of P in nodal rhythm of a heart without dextrocardia.

Fig. 3.—The mean electrical axis of P in cases of right auricular hypertrophy with nodal rhythm and without dextrocardia.

Fig. 4.—The mean electrical axis of P in cases of dextrocardia with nodal rhythm and without heart disease.

The ÂQRS in the standard leads was at −135°, or −45° if corrected for dextrocardia. The diagnosis of tricuspid atresia was made because of the combination of accentuated left axis deviation and the clinical finding of marked cyanosis. The postmortem study showed a dextroposition due to contracted pericardial adhesion which pulled the heart toward the right hemithorax. The marked right auricular hypertrophy explains the right deviation of the axis of P (ÂP) (compare with Fig. 3). On the other hand, a tetralogy of Fallot was evident. This finding will be dealt with later in the discussion on the QRS complex.

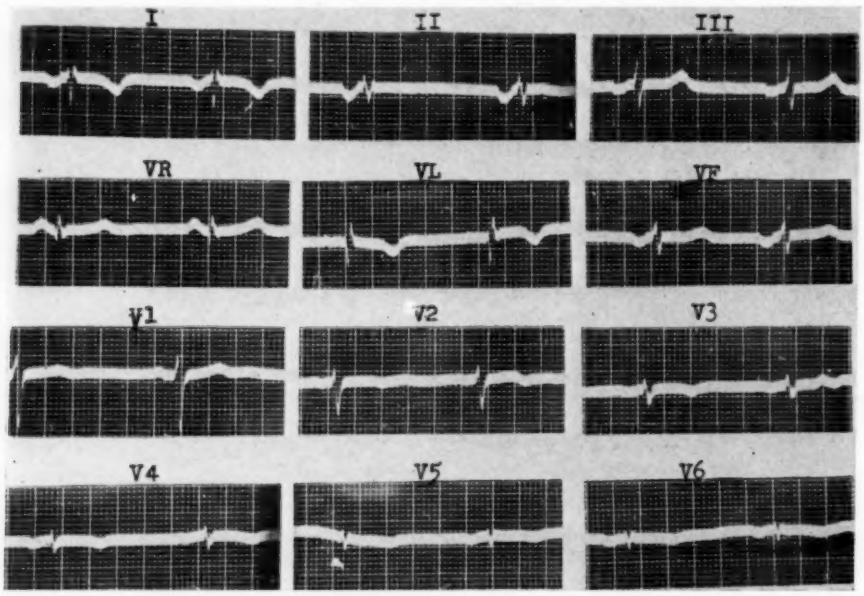

Fig. 5.—Tracing from a patient with dextrocardia and double mitral lesion. Note the P-wave changes due to rheumatic heart disease.

It must be borne in mind that there are other circumstances besides nodal rhythm which could account for negative P waves in Lead I, such as paroxysmal auricular tachycardia, auricular premature beats, and low auricular ectopic rhythms. The latter account for many of the clinical errors. Fig. 7 illustrates a case in which we made the diagnosis of nodal rhythm because of a negative P wave in Lead I as well as in Leads V_3 and V_6. All these findings led us to the diagnosis of transposition of the auricles (which diagnosis has not been confirmed by either clinical or radiologic studies), inasmuch as there was no situs inversus and the superior vena cava was located at the right side of the cardiac outline. This is probably a case of low auricular ectopic rhythm originating in the left atrium.

2. *Changes in the QRS Complex.*—Although changes in the QRS complex are well known, it is convenient to mention them again. (a) The classic mirror-image of QRS in Lead I is easily explained, since in dextrocardia the right auricle is oriented toward the left arm (Lead aVL) and the left chambers of the heart

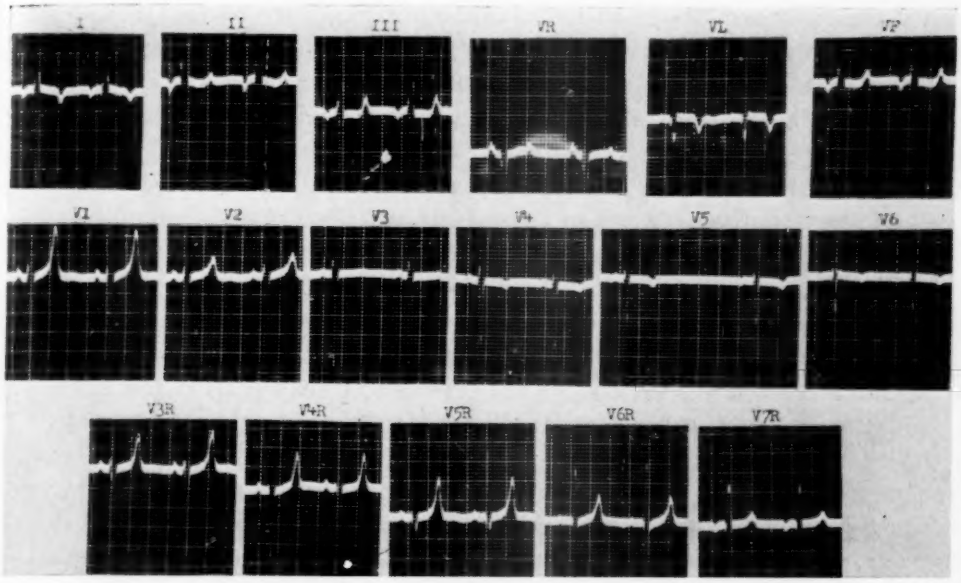

Fig. 6.—This tracing is very suggestive of dextrocardia with nodal rhythm and left ventricular hypertrophy. The postmortem study showed a dextroposition due to a contracted pericardial adhesion. The left cavities were normal, while the right ones were enlarged.

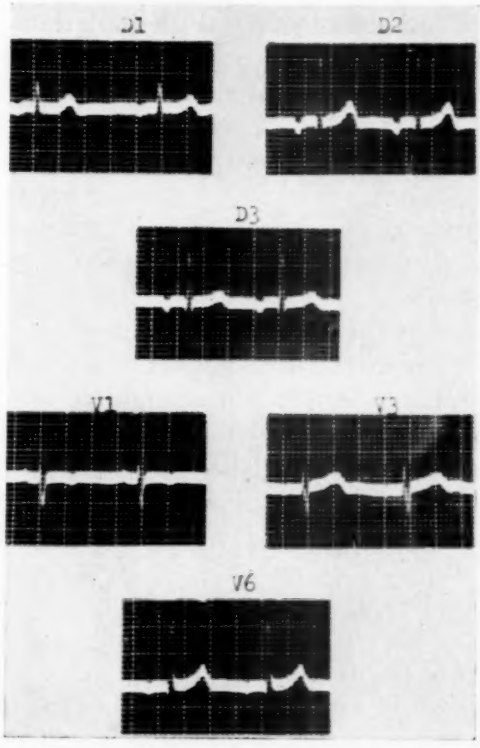

Fig. 7.—This tracing shows a low auricular ectopic rhythm which may erroneously suggest the diagnosis of auricular transposition.

toward the right arm (Lead aVR). Looking at Fig. 5 we find a QR and a negative T wave in Lead aVL which correspond to the variations in potential on the right auricular epicardium. (Do not confuse variations in potential with action potentials.) Lead aVR shows a qR or qRs ventricular complex, which indicates that the recording electrode is oriented toward the left ventricular portions, probably close to the left auricle. This is the reason for the rSr′ complex and the negative T wave in Lead I, which, if corrected from mirror-image, becomes qRs with a positive T wave. (b) Leads aVR and aVL, V_1 and V_2, and II and III are interchanged by reason of the transposition of both auricles and ventricles, as mentioned above. (c) It is obvious that the left precordial leads are interchanged with right ones (thoracic circle). (d) Usually, the left precordial leads V_3, V_4, V_5, and V_6 are oriented in dextrocardia toward the high or mid-portions of the right ventricle, and/or toward the right auricle. This is the reason for the progressive diminution of QRS voltage as the electrode changes from Lead V_1 to V_6. The rs morphologies recorded in Leads V_3 and V_4 in Fig. 5 look like those of the mid-portions of the anterior aspect of the right ventricle, while the M morphology of QRS in Leads V_5 and V_6 look like those of the higher portions of the right ventricle. On the other hand, in Fig. 1, Leads V_3, V_4, and V_5 show rS complexes similar to those found by Barbato and associates[2] on the epicardium of the right ventricle of the normal human heart; the QS morphology in Lead V_6 suggests that this lead is oriented toward the right auricle. (e) The right chest leads in dextrocardia have the following significance: Leads V_1R and V_2R usually record the variations in potential occurring on the trabecular zone of the right ventricle (Fig. 1); Leads V_3R (Fig. 1) and V_4R are oriented to the low interventricular septum; and Leads V_5R and V_6R manifest the free left ventricular wall. As stated before, the relationships between the exploring electrodes and the different aspects of the heart are true for a normal, relatively unrotated heart (Fig. 1). Exploring such an aspect of the heart means that the electrode records the variations in potential (Gaussian potential[1]) and not action potentials. It is also well known that any electrode registers all the vectors of the heart not perpendicular to the lead line.[1]

The spatial direction of QRS in authentic dextrocardia with situs inversus and without other cardiac anomalies: In a normal heart without dextrocardia the spatial direction of ÂQRS (SÂQRS) is from right to left, from the front to the back, and from above downward in intermediate or vertical hearts, and from below upward in the very horizontal hearts. In real dextrocardia there is a mirror-image of the normal direction of the SÂQRS; therefore, SÂQRS is directed to the right, behind, and downward or upward, depending upon the position of the heart. Positions at +120° are usual in the frontal plane, and when they are corrected, they correspond with a +60° position. This axis shows important modifications in ventricular hypertrophies, bundle branch blocks, myocardial infarctions, etc., and will be discussed later.

In the tracing shown in Fig. 1, ÂQRS is at +130° in Einthoven's triangle, and when this position is corrected (as if there were no dextrocardia), the axis becomes +50°. In the horizontal plane the transition zone is between Leads V_1 and V_3R, so that the vector points posteriorly and to the right. When this position is corrected, it will point posteriorly and to the left.

In Fig. 5, ÂQRS is around +150° in the frontal plane, and after correction it becomes +30°. It is impossible to determine accurately the position in the horizontal plane, although it seems to point backward and to the right, but when corrected it points backward and to the left.

3. *T Wave and ÂT in Real Dextrocardia With Situs Inversus and Without Other Cardiac Anomalies.*—The T wave is negative in Lead I; it is variable in Lead II, sometimes being inscribed negative, and sometimes positive. There is always a positive T wave in Lead III; it is positive in Lead aVF, negative in Lead aVL, and its direction in Lead aVR depends upon the position of the heart. It is positive in the right precordial leads; it may still be positive in the first left precordial leads, but when it approaches Leads V_4, V_5, and V_6, it becomes flattened or even negative.

The T wave becomes flat or negative in left precordial leads because of the fact that the more the electrode is moved toward the left precordium, the greater is the influence of the potential variations of the right ventricle and right atrium. A positive T wave in left precordial leads (V_5 and V_6) should be interpreted as abnormal, suggesting either a secondary change to left ventricular hypertrophy or incomplete left bundle branch block, or a primary change in repolarization, which could be due to either subepicardial ischemia of the free left ventricular wall or subendocardial ischemia of the left septal surface, or, less likely, right ventricular subendocardial ischemia.

The mean spatial axis of ventricular repolarization in true dextrocardia is directed from left to right, from up to down, and, generally, from back to front, which corresponds to a corrected SÂT pointing to the left, inferiorly and anteriorly.

In Fig. 1, ÂT is located at +150° in the frontal plane, and therefore at +30° after correction. In the horizontal plane the transition zone for the T wave is between Leads V_1 and V_3R, and as a result ÂT points slightly backward and to the right; after correction ÂT points backward and to the left.

In Fig. 5, ÂT is placed at +150°, which would correspond to +30° if no dextrocardia were present. In the horizontal plane, ÂT points to the right, but without deviations to the back or to the front. After correction it is directed to the left. These are two examples of SÂT that may be considered as normal.

We now present a case with dextrocardia and T-wave changes. Fig. 8 is illustrative of a patient with essential hypertension, arteriosclerotic heart disease, pulmonary emphysema, and coronary insufficiency. ÂT is located at −30° in the frontal plane, and when corrected it becomes −150°, which is definitely abnormal. In the horizontal plane the transition zone for T is between Leads V_2R and V_3R; here, ÂT points forward and to the left, which is definitely abnormal inasmuch as the corrected axis is directed anteriorly and to the right. Summarizing, after correction SÂT points upward, to the front, and to the right. In this example there is probably a combination of both primary and secondary T-wave changes. A secondary change can be considered because the tracing suggests left ventricular hypertrophy and first degree left bundle branch block. These conditions are usually associated with secondary changes of ventricular repolarization. The morphology of T in Leads V_3R and V_4R also suggests a

primary change, because the T wave is symmetrical and peaked, of the ischemic type, suggesting, in addition, the possibility of an apical infarct. The ventricular complex of the RS type with negative T wave suggests transmission of the left intracavitary potential to Lead V_3R in the presence of left bundle branch block.

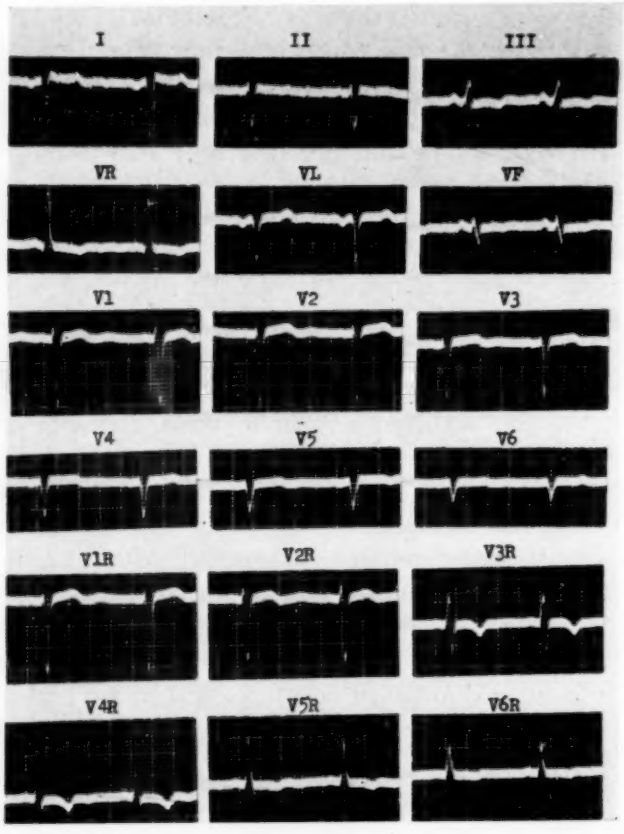

Fig. 8.—This tracing is from a patient with dextrocardia and essential hypertension. The tracing is very suggestive of incomplete LBBB, left ventricular hypertrophy, and myocardial infarction.

B. *Complicated Cases.*—In regard to the complicated cases it is important to comment on the diagnosis of atrial and ventricular enlargements, bundle branch blocks, and other abnormalities in the presence of real dextrocardia with situs inversus.

Real Dextrocardia With Left Atrial Enlargement.—As in the case of enlargement of the left atrium without dextrocardia, the P wave is broad (0.12 second or more), bifid, and often shows notchings and slurrings. If $\hat{A}P$ is located at $+120°$ in dextrocardia without atrial modifications, then, when there is left atrial hypertrophy or enlargement, $\hat{A}P$ will come to $-150°$ in the frontal plane. In the horizontal plane, $\hat{A}P$ points forward and to the right in noncomplicated dextrocardia, but if there is left atrial enlargement, it will be directed backward and to the right. In summary, when there is significant enlargement of the left atrium $S\hat{A}P$ is directed superiorly, posteriorly, and to the right.

The tracing shown in Fig. 5 was recorded on a patient with "pure" mitral stenosis; ÂP is located at −120° in the frontal plane. In the horizontal plane the transition zone is at Lead V_3, and the P wave is negative from Lead V_4 to V_6. This is a good example of ÂP directed to the right, upward and backward. Besides, the P wave shows slurrings in Leads I and II and it is widened to 0.12 second in Lead II.

Real Dextrocardia With Right Atrial Enlargement.—When there is enlargement of the right atrium without dextrocardia, the P wave becomes tall and peaked and its duration is normal. These changes appear in Leads II, III, and aVF. ÂP becomes vertical and is located at about +80°. In the horizontal plane the ÂP points anteriorly and slightly to the left.

If a real dextrocardia with right atrial enlargement exists, the P-wave changes are also recorded in Leads II, III, and aVF, since Leads II and III are interchanged. ÂP would be at about +100° in the frontal plane, while it would point anteriorly and to the right in the horizontal plane.

Real Dextrocardia With Enlargement of Both Atria.—ÂP may be at +120°, which is its normal location in dextrocardia, or it may be deviated to the left (near +90°) or to the right (near +180°) according to the particular predominant atrial enlargement. The P wave is not only tall and peaked but its duration increases from 0.12 to 0.13 second or more. The recognition of dextrocardia is not difficult, since the P wave remains negative in Leads I and aVL, and positive in Lead aVR.

The Diagnosis of Atrial Enlargement by the QRS Complex in Real Dextrocardia.—It has been shown in previous publications[3] that the QRS complex may be of great help in the recognition of right or left atrial enlargement. This is also true in real dextrocardia. QR complexes with or without right bundle branch block in Leads V_2, V_1, V_3R, etc., are very suggestive of right atrial enlargement complicating a real dextrocardia when a myocardial infarct can be ruled out; this morphology is frequent in rheumatic mitrotricuspid valvular disease, chronic cor pulmonale, or pulmonary embolism (acute cor pulmonale).

Less frequently, a Q wave may be present in those leads exploring the left ventricle (Leads V_5R and V_6R), and in the absence of myocardial infarction such a Q wave suggests a huge left atrium in patients with rheumatic heart disease.[1]

Real Dextrocardia With Ventricular Enlargement.—In the presence of ventricular hypertrophies complicated by real dextrocardia and situs inversus it is difficult to recognize whether the pattern obtained is the result of the left or right ventricular enlargement. There is an increase in the R wave and a decrease in the S wave in the QRS complex of the enlarged ventricle. The problem is difficult because complexes of the qR, Rs, and rsR types may correspond to enlargement of either ventricle. We must keep in mind the fact that real dextrocardia with transposition of the atria and the great vessels but without transposition of the ventricles can occur (dextrocardia with "corrected" transposition of the great vessels).

A careful study of Fig. 9 makes the diagnosis of atrial transposition relatively easy, since the P wave is negative in Leads I and aVL, slightly diphasic

in Lead aVR, and decreases in voltage from Leads V_1 to V_6, being flatter in Lead V_6. The complexes are of the qR type from Lead V_2 to V_6, and it must be decided whether they correspond to right or left ventricular complexes. This differential diagnosis can be reached by a consideration of the following points.

Differential Diagnosis Between Right and Left Ventricular Hypertrophy in Dextrocardia With Atrial Transposition and With or Without Ventricular Transposition.—(1) In left ventricular hypertrophies the transitional complexes are often absent, with a sudden change from negative rS right ventricular complexes to positive qR, Rs, qRs, or R left ventricular complexes. (2) Transitional isodiphasic complexes (RS) in several leads are suggestive of right ventricular hypertrophy. The positive complexes, therefore, probably belong to the right ventricle, and those which are negative (rS and qrS) correspond to the left ventricle. (3) If rS complexes are obtained in several precordial leads, they most probably correspond to the right ventricular trabecular zone and, then, to right ventricular enlargement. (4) The tracing suggests right ventricular hypertrophy if in the same leads the P wave is positive, peaked and tall, and the ventricular complexes are also positive. (5) The tracing suggests left ventricular hypertrophy if in the same lead the P wave is positive and broad (0.12 second or more) and the ventricular complexes are also positive (frequently qR type). (6) The T wave is usually negative in left ventricular leads in the presence of left ventricular hypertrophy, while it may be either positive or negative in right ventricular leads in the presence of right ventricular hypertrophy.

Fig. 9 should be reviewed with the foregoing data in mind. It should be noted that the highest P wave is in Lead V_1, and that the voltage of P diminishes to the left precordial leads; on the other hand, ventricular complexes are essentially positive: qR from Lead V_2 to V_6. These findings suggest that the positive morphologies belong to the left ventricle. Complexes of the rS type are found at Points 9, 10, and 11 in the thoracic circle (Fig. 9), and may correspond to the right ventricular trabecular zone. The isodiphasic complexes at Point 12 and in Lead V_1 correspond probably to the interventricular septum. Once the left ventricle has been identified, the tracing becomes suggestive of left ventricular hypertrophy because $\hat{A}QRS$ is at 0°, and because there is marked counterclockwise rotation since the left ventricular morphologies are present from Lead V_2 to V_6. Besides, the positive complexes which, according to the preceding discussion, belong to the left ventricle are found from Point 1 to Point 7, that is, they occupy a whole hemithorax, thus indicating marked left ventricular enlargement. In this case, postmortem study revealed dextrocardia, situs inversus, atrial transposition, transposition of the great vessels, and a left ventricle on the left side and right ventricle on the right ("corrected" transposition of the great vessels).

Bundle Branch Block in Real Dextrocardia.—A knowledge of the unipolar morphologies in both left and right bundle branch block is most important in diagnosing real dextrocardia and other changes of heart position.

1. *Real dextrocardias with RBBB:* An rsR complex and negative T-wave pattern is usually obtained in Leads V_1 and V_2. This morphology reflects the variations in potential of the free right ventricular wall. Lead V_3R reflects the

variations in potential of the trabecular zone of the right ventricle where an rsR′S′ complex with negative T wave is often recorded, and Lead V_4R is oriented toward the low portion of the interventricular septum where an RS with negative T-wave pattern is usually recorded. On the other hand, Leads V_5R and V_6R register the variations in potential of the left ventricular wall, that is, the unipolar morphology is of the qRs type with positive T wave. Along with this knowledge of the unipolar morphologies of RBBB, we must also consider the changes produced by other pathology in addition to the block. This additional information goes beyond the scope of this paper, but a simple example may be given: the findings of qR complexes in Leads V_2 and V_1, followed by rSR in Leads V_3R and V_4R, should suggest the presence of an important enlargement of the right atrium[3]; on the other hand, if the Q wave is found in Leads V_3R and V_4R, an infarct of the interventricular septum is more likely than a right atrial enlargement.

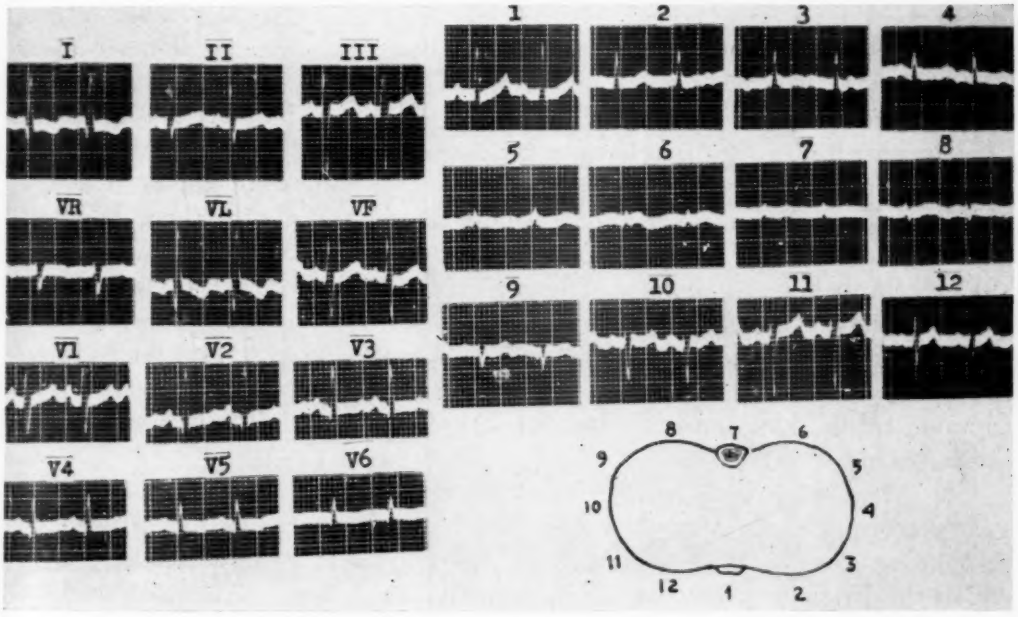

Fig. 9.—This tracing is from a patient with dextrocardia and atrial transposition. The left ventricle was on the left side and the right ventricle on the right ("corrected" transposition of the great vessels).

Uncomplicated RBBB complexes in left precordial leads (V_3, V_4, V_5, and V_6) may represent either the variations in potential of the right ventricle or those of the right atrium. Two examples of this are shown in Figs. 10 and 11, which were recorded on the same patient. The tracings are typical of real dextrocardia complicated by incomplete RBBB. The M type of QRS complexes with two positivities and negative T wave are present in Leads V_1R and V_2R (Fig. 10), while in Leads V_3R and V_4R the morphologies are RS with negative or diphasic T wave corresponding to the low septal portions. In Leads V_5R and V_6R the qRs morphologies represent the variations in potential of the left ventricle. In

Fig. 11, right ventricular morphologies are also obtained in left precordial leads (V_3 and V_4), thus suggesting an enlargement of the right ventricle. The morphologies in Leads V_5 and V_6 correspond either to the right atrium or to those higher portions of the right ventricle which are closer to the atrioventricular groove. All these findings are in agreement with the clinical diagnosis of double mitral lesion.

Fig. 12 is an important illustration of many of the concepts set forth in this report. The P wave is inscribed after QRS (low nodal rhythm) and is positive in Leads I and aVL, and negative in Leads II, III, and aVF; this means that $\hat{A}P$ is located at $-60°$ in the frontal plane, suggesting a nodal rhythm without transposition of the atria, inasmuch as a nodal rhythm in real dextrocardia should result in an $\hat{A}P$ located at $-120°$.

The finding of a negative P wave in Leads V_4R and V_6R suggests also that the right atrium is on the right side, unless there is a hypertrophied right atrium located on the left side. The tracing suggests incomplete right bundle branch block, and the QR morphology (with slurred R) found in Leads I and aVL corresponds to the right atrium; therefore, it is demonstrated that there is a large left-sided right atrium.

The morphology in Lead aVR (RS with slurred R) is typical of the variations in potential of the free left ventricular wall in RBBB, and indicates that the left ventricle is right sided. The left precordial morphologies (Leads V_1 to V_6) correspond to the variations in potential of the right atrium; Lead V_3R probably has a low septal morphology, and the morphologies in Leads V_4R and V_6R are probably also septal. This was the case in which the electrocardiographic diagnosis of transposition of the cavities was not easily accepted, since no viscerum situs inversus was present. The angiocardiographic study proved the transposition of the four chambers, and the final clinical diagnosis was a common trunk, with the heart located in the right side without viscerum situs inversus (Fig. 13).

2. *Real dextrocardias with LBBB:* A similar analysis is made for LBBB. Left precordial leads (V_1 to V_6) show a QS complex with positive T wave corresponding to either right ventricle or right atrium. The morphology is also registered in right precordial leads, usually until Lead V_4R; then suddenly there is a change in morphology from Lead V_4R to V_5R, and in the latter as well as in Lead V_6R there is a left ventricular morphology with a broad R showing notching and slurring at the top and a negative T wave.

Real Dextrocardia With Myocardial Infarction.—The diagnosis of myocardial infarction should follow the general rules. For instance, an anteroseptal myocardial infarction will be apparent in Leads V_2, V_1, V_3R, and V_4R; an anterolateral one will be manifested in Leads V_4R, V_5R, and V_6R. The posteroinferior infarct will be recognized in Leads II, III, and aVF, but the signs are less marked in Lead III than in Lead II, etc.

Fig. 8 shows the tracing of a patient with dextrocardia and incomplete LBBB. The block is recognized because of the absence of a Q wave in Leads V_3R, V_4R, V_5R, and V_6R, as well as by slurring in both the upstroke and downstroke of the R wave in the same leads. Leads V_3R and V_4R show a negative,

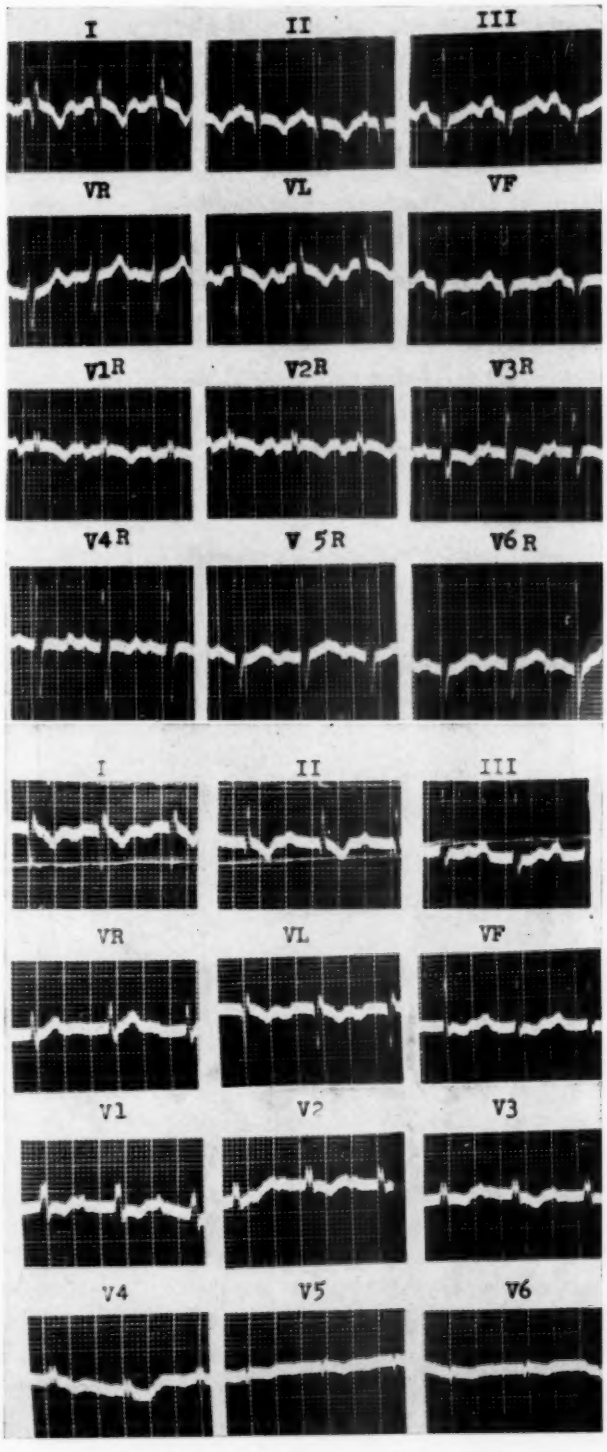

Fig. 10.

Fig. 11.

Fig. 10.—Right bundle branch block complicated by dextrocardia. Note that the potential variations of the free left ventricular wall are recorded in Leads V_5R and V_6R.

Fig. 11.—This tracing was recorded on the same patient as in Fig. 10. Note that the variations in potential of the free right ventricular wall are recorded from Lead V_1 through Lead V_4.

symmetrical, peaked T wave of the so-called ischemic type, which might or might not be due to myocardial infarction; nevertheless, the RS complex with negative T in Lead V_3R suggests the possibility that this lead is recording through a transmural myocardial infarction the intracavitary left ventricular potential, which is of the RS type with negative T in LBBB.

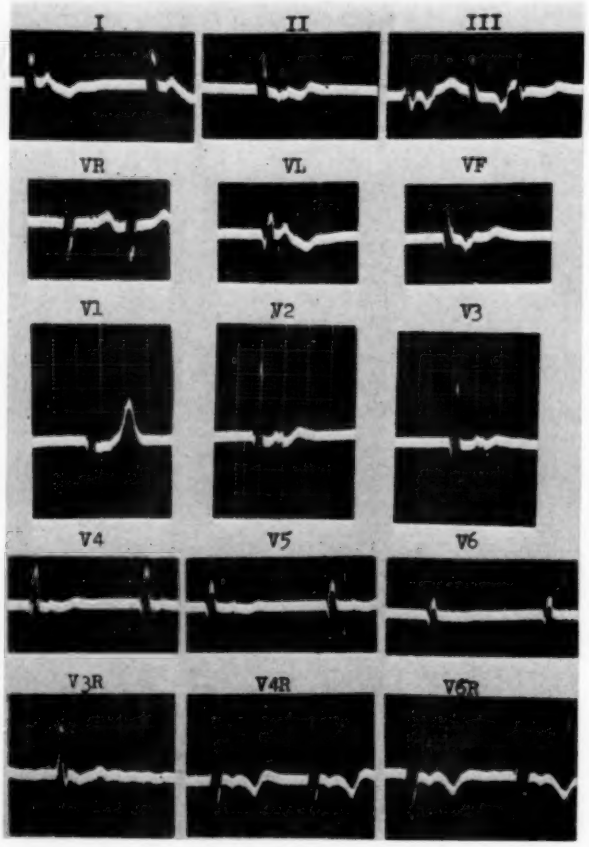

Fig. 12.—This tracing suggests transposition of the cavities because the variations in potential of the free left ventricular wall in the presence of incomplete RBBB are recorded in Lead aVR. There is also an infranodal rhythm.

II. DEXTROROTATION

In dextrorotation the heart is placed in the right chest but the cavities keep their normal relationship: the left ventricle is left sided, and the right ventricle is right sided, while the apex is directed to the right. This anomaly is much less frequent than real dextrocardia. Usually, dextrorotation is associated with severe cardiac malformations but it may be present in normal hearts. Campbell and Reynolds[4] found 15 cases of dextrorotation, all complicated by congenital malformations. Lichtman[5] reviewed 161 cases and only 3 had no associated anomalies. In postmortem studies Taussig (quoted from Nadas[6]) found that single ventricle is the most common anomaly complicating dextrorotation.

Cases of dextrorotation do not show the electrocardiographic mirror-pattern described for dextrocardia with transposition of the cavities. Of the 15 cases described by Campbell and Reynolds, 12 had a positive P_1, while it was negative in the other 3. Therefore, P_1, P_2, and P_3 are usually positive.

Electrocardiographic Findings That Aid the Recognition of Dextrorotation.—

1. *P wave and ÂP:* The P wave is usually positive in the standard leads, and in most cases it does not help in reaching the diagnosis of dextrorotation. In some tracings, however, the following findings in Lead I may be of great help: (a) diphasic P waves of the minus-plus (−+) type, (b) low P waves, (c) negative P, and (d) negative P with nodal rhythm. But if the P wave is positive in the left precordial or thoracic leads, the diagnosis of atrial transposition can be ruled out. A positive P wave in Leads V_4, V_5, and V_6 is hardly compatible with the diagnosis of atrial transposition. The negativity of the atrial wave in Lead I might probably be due to a great right atrial enlargement, to dextrorotation, or the combination of both.

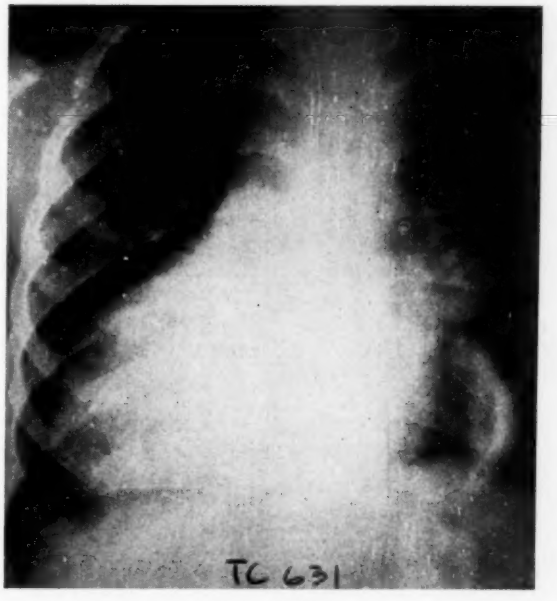

Fig. 13.—Radiographic study of the case discussed in Fig. 12. The clinical diagnosis was a common trunk, with the heart located in the right side without viscerum situs inversus.

In the tracing shown in Fig. 14, P has a slight initial negativity in Lead I (−+), suggesting dextrorotation. Atrial transposition is definitely ruled out because the P wave is more positive in Lead V_6 than in Lead V_1.

The tracing reproduced in Fig. 6 is more complicated. The negative P waves corresponding to nodal rhythm which are present in all three standard leads strongly suggest the possibility of a true dextrocardia. The diagnosis of this latter anomaly would seem reinforced by the positive P in Lead V_4 becoming diphasic in Lead V_5 and negative in Lead V_6. The only possible doubt arising in this diagnosis would be that due to the negative P in Lead V_7R. The inter-

pretation of this tracing is difficult and leads to an erroneous diagnosis of real dextrocardia with left ventricular enlargement.

It should not be overlooked that transient atrial ectopic rhythms are relatively common in dextrocardia and dextrorotation, and this fact increases the confusion in interpretations. In the tracing of Fig. 15 the P wave is positive in Lead V_5, negative in Lead V_6, and positive in Lead V_7, indicating that in Lead V_6 a transitory atrial rhythm was recorded.

2. *QRS complex and ÂQRS:* An understanding of unipolar morphologies in normal cases, in ventricular hypertrophies, and in bundle branch blocks will again be of help in determining the location of the ventricles.

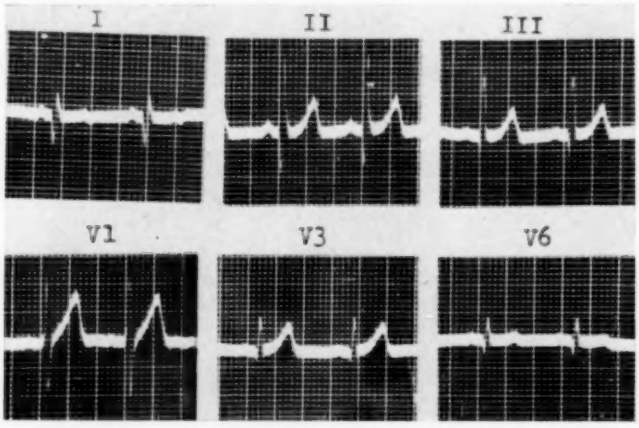

Fig. 14.—This tracing is from a heart with dextrorotation. Note the deep Q wave in Lead I, the left ventricular morphologies in Lead V_3, and the transitional or septal morphology in Lead V_1.

Further Indications of Dextrorotation.—Dextrorotation could be suspected in the following instances:

1. When the left ventricular morphologies are located in the precordium more to the right than usual and the transitional septal morphologies are closer to Lead V_1. In Fig. 16 there is ÂQRS deviation to the left with ÂT to the right (ÂQRS = 0°; ÂT = +165°), suggesting enlargement of the left ventricle. The QRS morphology in Leads V_5 and V_6 suggest some degree of incomplete left bundle branch block, reinforcing the diagnosis of left ventricular hypertrophy. Left ventricular morphologies are present from Lead V_2 to V_6, and septal morphologies appear in Lead V_1. These findings speak in favor of important dextrorotation. It is necessary to make clear that the term dextrorotation in congenital heart disease is not applied to rotations on the longitudinal axis of the heart, but to rotations on the anteroposterior axis. The fact that the left ventricular morphologies are recognized from Leads V_2 to V_6 in Fig. 16 suggests levorotation on the longitudinal axis; but the recognition of septal morphology in Lead V_1 is not easily explained by levorotation, and suggests a dextrorotation on the anteroposterior axis. The patient had tricuspid atresia, and the heart was in the right side of the chest.

2. When the pattern of the trabecular zone of the right ventricle is recorded more to the right than usual and the morphologies of the right ventricle are still inscribed near the right mid-axillary line. In Fig. 17 the rS complex corresponding to the trabecular zone is registered not only from Lead V_1 through V_4 but also in Lead V_3R. At the same time the RS complexes (not to be confused with septal morphologies) belonging to the middle portions of the free right ventricular wall are obtained in Leads V_4R and V_5R, and those from the upper portions of the same free right ventricular wall (Rs in the presence of right ventricular hypertrophy) are obtained in Lead V_6R. If the question arises as to whether the latter morphologies belong to the left ventricle, the answer would be no. The reason is that in Lead aVR the P wave is mainly negative. That is, Lead aVR is recording the variations in potential of the right atrium; in the same lead, QRS is mainly positive (R type with negative T), and therefore the diagnosis of right ventricular hypertrophy must be suggested. This tracing was recorded

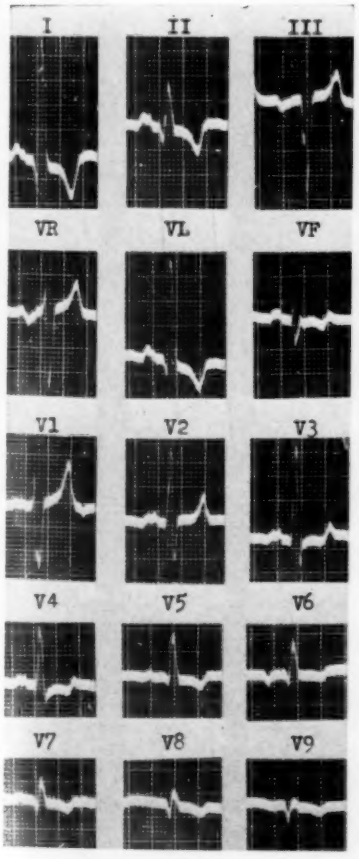

Fig. 15.

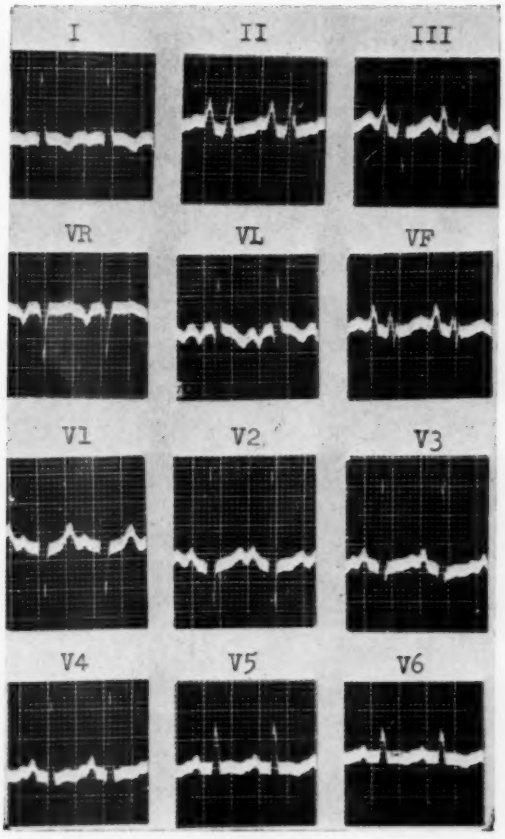

Fig. 16.

Fig. 15.—This tracing corresponds to a heart with dextrorotation and tricuspid atresia. Note the left ventricular morphology in Lead V_3 and the left auricular morphology in Lead V_6. The negative P wave in this lead corresponds to a transitory atrial rhythm.

Fig. 16.—This tracing corresponds to a heart with dextrorotation and tricuspid atresia. Note the septal transitional morphologies in Lead V_1 and the left ventricular morphologies from Lead V_2 to V_6.

on a patient with trilogy of Fallot and a right-sided heart. The catheterization performed on this patient showed the right ventricular pressure to be greater than the systemic pressure.

3. When the left ventricular unipolar morphologies in Leads V_5, V_6, and V_7 correspond or suggest the proximity of the left atrium. Fig. 15 shows a tracing in which the data strongly suggest left atrial and left ventricular enlargement. A wide and deep Q wave and a negative T wave are registered in Leads V_5, V_6, and V_7, suggesting the proximity of the left atrium. Normally, these morphologies are registered in posterior thoracic leads, and their displacement to the right (there is also left ventricular morphology in Lead V_3) suggests dextrorotation on the anteroposterior axis. The patient suffered from tricuspid atresia and a right-sided heart.

4. Whether Qr complexes in Lead I are associated, or not, with a deep Q wave in Leads II and III. These morphologies with a deep Q wave probably

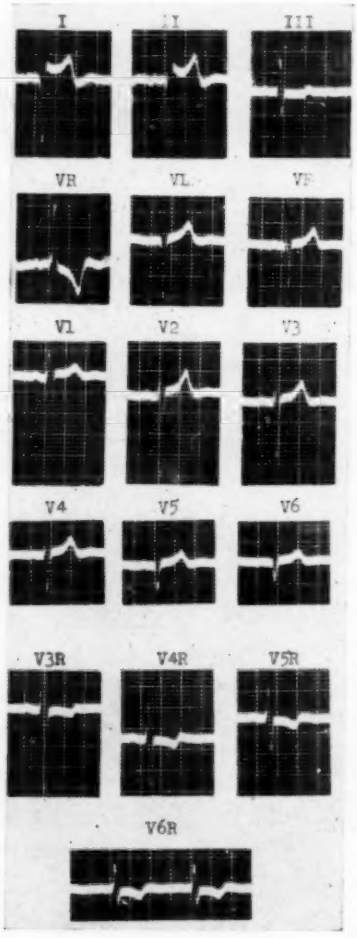

Fig. 17.—The tracing corresponds to a heart with dextrorotation and trilogy of Fallot. Note that the small rS complexes belonging to the trabecular zone are registered in Lead V_3R, and the Rs patterns of the free right ventricular wall are obtained in Lead V_6R.

correspond to the variations in potential of the left atrium which are transmitted to Lead aVL because of the dextrorotation. In the tracing shown in Fig. 14 the complex in Lead I is of the QR type, while in Lead V_6 the Q wave is deeper than in Lead V_3. All these changes suggest the influence of left atrial morphologies. On the other hand, Lead V_3 shows left ventricular morphology, while Lead V_1 has septal morphology. This is a typical example of the displacement of all the morphologies toward the right precordial leads. The complex in Lead V_1 should not suggest right ventricular hypertrophy, because it is only a septal morphology displaced to the right. It is indeed more convenient to understand a tracing than to make the routine measurements.

III. DEXTROPOSITION

In dextroposition the heart is pulled or pushed to the right; therefore, this condition cannot be a real congenital postural anomaly of the heart. The ventricles keep their normal relationship, that is, the left ventricle is on the left and the right ventricle is on the right, with the apex usually pointing to the left. Dextroposition is usually caused by an acquired condition such as atelectasis of the right lung, right-sided retractile pleural fibrosis, massive left pleural effusion, etc., but it also may be due to an extracardiac congenital disease such as agenesia of the right lung, or, less frequently, any of the above-mentioned conditions complicating a congenital heart malformation.

The electrocardiographic findings will be identical to those described for dextrorotation. Of course, a pneumothorax or a pleural effusion will be associated with low voltage in the leads exploring points close to them.

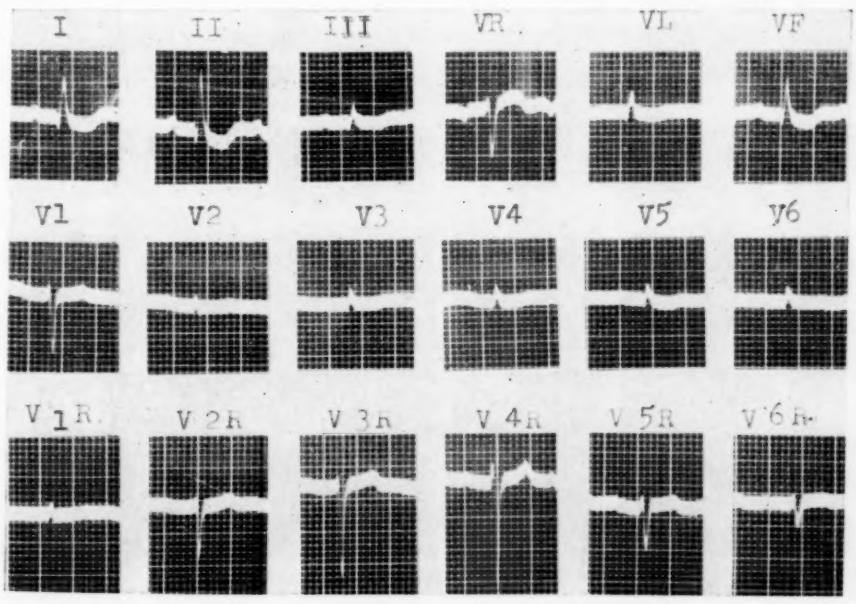

Fig. 18.—This tracing is very suggestive of cardiac dextroposition, because the left ventricular morphologies are present from Lead V_3 to V_6. The low voltage in these leads, as compared with the others, is compatible with a left pleural effusion.

The tracing shown in Fig. 18 is highly suggestive of cardiac dextroposition. Left ventricular morphologies are present in the three standard leads, in Leads aVL and aVF, and also from Lead V_3 to V_6, while a morphology from the trabecular zone of the right ventricle is obtained in Lead V_1 and in the other right precordial leads, thus indicating a cardiac displacement to the right. The low voltage from Lead V_2 to V_6 as compared to the voltage in the right leads (the inverse is usually normal) may be compatible with the presence of a massive left pleural effusion. Roentgenologic studies demonstrated the presence of such effusion which produced a massive atelectasis of the left lung.

IV. LEVOCARDIA

In levocardia there is situs inversus but the heart stays in its normal location in the left chest, with the apex pointing to the left. It is a rare condition.

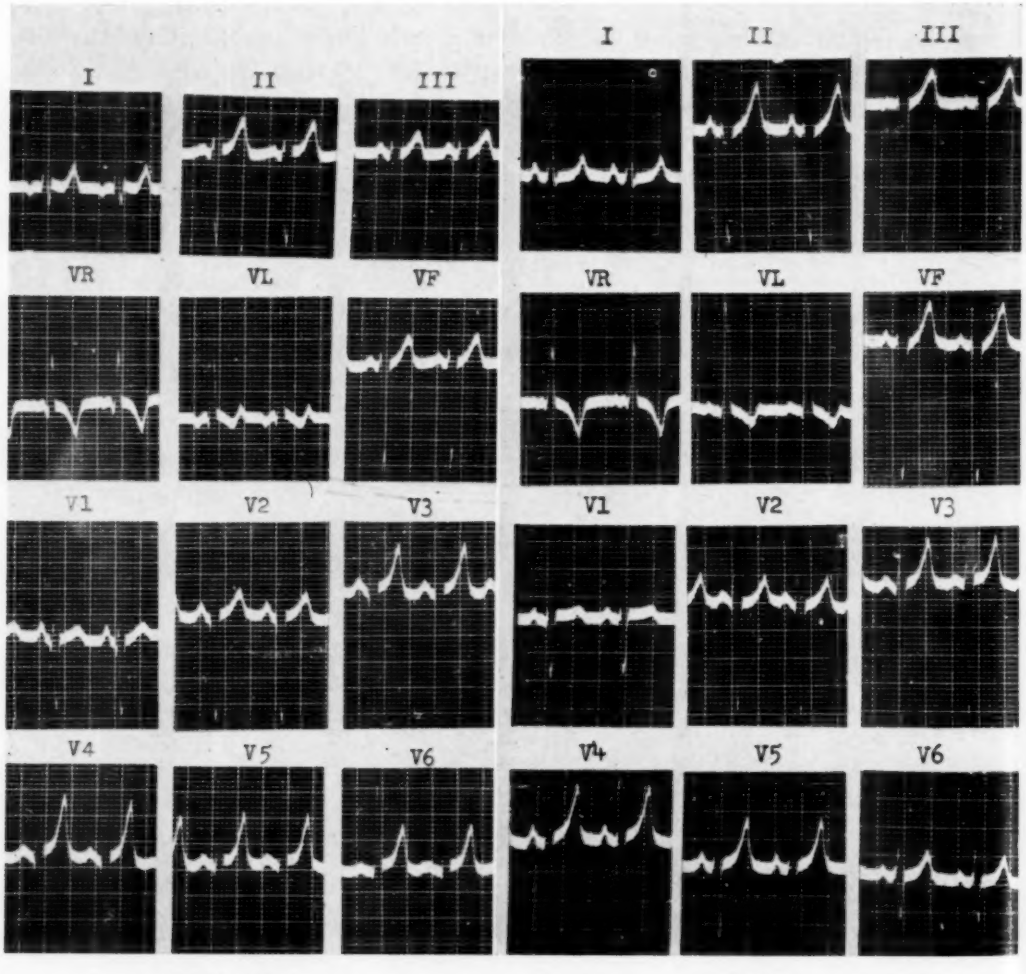

Fig. 19. Fig. 20.

Fig. 19.—This tracing is from a heart with levocardia. Note the negative P wave in Lead I, due to an ectopic auricular rhythm inasmuch as a few weeks later the P wave become positive (see Fig. 20).

Fig. 20.—This tracing is from the same case as that discussed in Fig. 19.

Doliopoulos and Maillet[7] found 34 cases reported in the literature, and described 5 cases of their own. In 900 cases of congenital heart disease at the Hospital Broussais in Paris, 5 levocardias were found (0.55 per cent).

Levocardia is always complicated by very complex congenital malformations. In the review made by Doliopoulos and Maillet, 95 per cent of the 39 cases were cyanotic. Campbell and Reynolds[4] found 14 levocardias, all complicated by other malformations (12 cyanotic, 2 acyanotic). Among the malformations most commonly associated with levocardia is atrial transposition, as has been observed by Forgacs[8] and others. Young and Griswold[9] pointed out the frequent transposition of the atria and the great vessels.

Electrocardiographically, there are frequent atrial arrhythmias that may produce a negative P wave in Lead I and erroneously suggest the diagnosis of atrial transposition. This is exemplified by the tracings shown in Figs. 19 and 20, in which a situs inversus was proved although the heart was in the left side. The negative P wave in Lead I (Fig. 19) led us to believe that the right atrium was placed in the left side, as did the voltage lowering of P from Lead V_1 to V_6. A few weeks later the rhythm changed (Fig. 20). P became positive in Lead I and the voltage of P increased in Lead V_6; catheterization and angiocardiography demonstrated that the right atrium was in its proper place.

Inasmuch as in 50 per cent of the cases of levocardia there is transposition of the auricles, we can apply the same information about the P wave as in regard to real dextrocardia (see above).

From the foregoing we can state that the diagnosis of levocardia is made on a clinical basis rather than by the electrocardiogram; but the latter aids in the recognition of transposition of the cavities (if transposition is present) as well as other anomalies, such as hypertrophies, blocks, etc. Perhaps the only tracing directly suggestive of levocardia would be that with atrial transposition (negative P in Lead I) with no ventricular transposition (normal QRS), since atrial transposition alone is rare in dextrocardia and frequent in levocardia.

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Reflex Venoconstrictor Response to Strong Autonomic Stimulation

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The venous system is provided with smooth muscle and autonomic innervation,[1] and a large part of the total blood volume lies within this venous system. There is much evidence that neurogenic venomotor tone and reflex venomotor reactions exist and are important in over-all circulatory regulation, in both health and disease.[1-4] Duggan, Love, and Lyons[4] presented evidence that the efferent nerves mediating these reactions are in the sympathetic nervous system in man, just as venomotor fibers were found to be present in the sympathetic system in animals.[5] It has been pointed out that an elevation of the central venous pressure (CVP) occurring in response to a stimulus which also causes superficial venoconstriction suggests that venoconstriction has been widespread enough to cause the over-all rise in pressure.[2] The amount of rise in central venous pressure, then, constitutes some measure of general venoconstrictor response. Over-all venoconstriction might be mediated humorally or by reflex action.[6] If a strong stimulus capable of causing venoconstriction were abruptly applied, the time required for development of the response might differentiate between these two pathways. Development of a response within less than 10 seconds would strongly favor reflex rather than humoral mediation. Electroshock therapy (EST) provides a strong, abrupt autonomic stimulation.

The purpose of this investigation was to determine the extent and time course of the rise in central venous pressure which occurred when the autonomic system was strongly stimulated by electroshock therapy.

METHODS AND MATERIALS

Subjects.—The subjects used in this study were 11 physically normal psychiatric patients who had a variety of psychiatric diagnoses for which they were receiving a course of electroshock therapy.

Medications.—The patients received from 0.8 to 1.2 mg. of atropine sulfate intramuscularly prior to the time of therapy. Immediately before the EST, most patients were given intravenous

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thiopental in a sufficient quantity to abolish the wink reflex, and all patients were given intravenous succinylcholine in dosages varying from 15 to 60 mg., which allowed only a minimal motor response. They were then respired on 100 per cent oxygen from a bag by an anesthetist, so that anoxia did not play a part in the results obtained.[7]

Central Venous Pressure.—When the patients arrived in the therapy room, a small polyethylene catheter was inserted into an antecubital vein through a No. 16 thin-walled needle. The catheter was advanced the distance estimated necessary for the end to be placed in the superior vena cava. Central venous pressure was measured through the catheter and recorded by a Brush direct-writing recording system, using a Statham strain gauge (0-25 mm. Hg) as transducer. Base-line central venous pressure was recorded before the thiopental was given. Then, a continuous recording of central venous pressure was made until thiopental, succinylcholine, oxygen, and EST were given, and for several minutes following the EST.

Electroshock Therapy.—The electroshock therapy given was one of three types. Six patients received stimulation for a duration of 0.3 to 0.7 second with a Medcraft electroshock machine. Three were given stimulation of 5 seconds' duration with a Liberson brief stimulus therapy apparatus. Two patients were given stimulation for durations of 60 to 90 seconds with a Reiter apparatus.

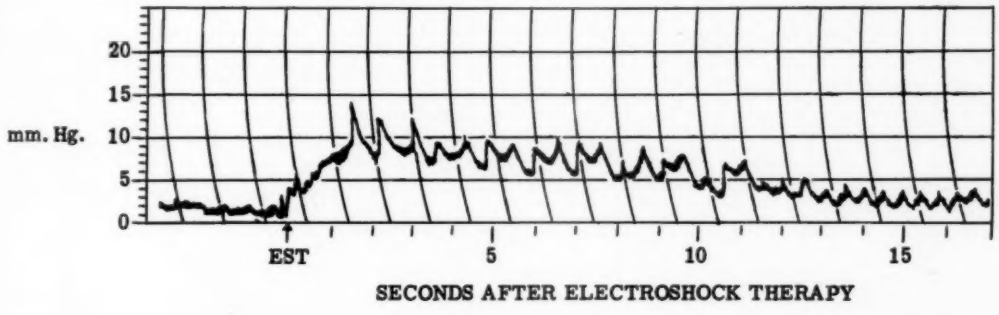

Fig. 1.—Response of central venous pressure to electroshock stimulation. This patient (J.D.) had EST for a duration of 0.5 second, with an increase in CVP beginning within 1 second after EST was begun. Mean increase in CVP within 10 seconds was 6.5 mm. Hg, the maximum rise occurring around 5 seconds after the stimulation was begun.

RESULTS

Central venous pressure was measured in 11 patients, and there was a significant rise in CVP, either during or following the EST, in 10 patients.

Nine patients received EST for a duration of 5 seconds or less, and an increased central venous pressure was observed in 8 of these (Table I). A typical recording of central venous pressure is presented in Fig. 1. In every one of the 8 patients in whom an increased central pressure was observed the rise began almost immediately, that is, within less than 5 seconds after the EST was begun. Muscle movements were virtually absent or consisted of mild tensing during application of EST. Such motion as did occur had no evident effect on central venous pressure, and the major rise in pressure occurred after shock, when the subjects were relaxed. A substantial increase in central venous pressure developed after cessation of shock, so that the effect of muscular tensing was excluded, but within 10 seconds after onset of the electrical stimulus, presumably too soon for mediation of venoconstriction by a circulating humoral agent. The increase in central venous pressure during this first 10 seconds amounted to between

40 and 100 per cent of the maximum pressure rise which occurred in the patients of this group. The mean maximal increase in central venous pressure in these patients was 5.4± 2.4 mm. Hg. In 6 of the patients the maximal rise in central venous pressure occurred within 20 seconds after the start of EST. In one patient the peak central venous pressure occurred after 1 minute, and in the other patient the maximal rise in central venous pressure occurred 2 minutes after EST was given. The central venous pressure remained above the resting level for as long as 3 minutes after the EST in 6 patients.

Two patients were given EST for durations of 60 to 90 seconds, and each was studied on two different occasions (Table II). A rise in central venous pressure was noted immediately after EST was begun in all four trials. The mean maximal increase in central venous pressure was 13.0± 3.1 mm. Hg, and the peak occurred from 50 to 120 seconds after the EST was begun. The greatest individual rise in pressure amounted to 15.9 mm. Hg above the resting level (Table II).

TABLE I. CHANGES IN CENTRAL VENOUS PRESSURE (CVP) IN 9 PATIENTS WHO RECEIVED ELECTROSHOCK THERAPY (EST) FOR A DURATION OF 5 SECONDS OR LESS

SUBJECT	DURATION OF EST (SEC.)	ONSET OF RESPONSE* (SEC.)	RESPONSE WITHIN 10 SEC.† (MM. Hg)	MAXIMUM RISE IN CVP		ELEVATION OF CVP MAINTAINED 3 MIN. AFTER EST
				AMOUNT (MM. Hg)	TIME‡ (SEC.)	
J.D.	0.3–0.7	1	6.5	6.5	5	No
H.R.	0.3–0.7	2	3.4	8.2	120	Yes
J.M.	0.3–0.7	2	5.8	7.6	15	No
C.Y.	0.3–0.7	3	3.9	3.9	10	Yes
A.W.	0.3–0.7	2	3.6	6.1	60	Yes
F.R.	0.3–0.7	3	5.5	5.5	10	Yes
O.B.	5	3	5.5	6.2	20	Yes
R.C.	5	No Rise	0	0	No Rise	No
P.T.	5	5	2.6	4.9	20	Yes
Mean			4.1±2.0	5.4±2.4		

TABLE II. CHANGES IN CENTRAL VENOUS PRESSURE (CVP) IN 2 PATIENTS WHO RECEIVED ELECTROSHOCK THERAPY (EST) FOR DURATIONS OF 60 TO 90 SECONDS

SUBJECT	ONSET OF RESPONSE* (SEC.)	MAXIMUM RISE IN CVP	
		AMOUNT (MM. Hg)	TIME‡ (SEC.)
D.C.	(a) 1	13.6	60
	(b) 1	8.7	120
K.W.	(a) 1	15.9	90
	(b) 1	13.7	50
Mean		13.0±3.1	

*The time by which a definite CVP response is evident, measured from the start of EST.
†Maximum rise in CVP within 10 seconds after the start of EST, but not during application of EST.
‡Measured from the start of EST.

DISCUSSION

The results indicate a very strong venoconstrictor response to stimulation by electroshock therapy. The rises in central venous pressure which occurred are of sufficient magnitude to suggest a considerable over-all increase in peripheral venous tone. The increase in central venous pressure which can be produced is similar in magnitude to that which occurs with congestive heart failure. Table III shows increases in central venous pressure which have been produced by other methods of stimulating the autonomic nervous system.

The time course of the rise in central venous pressure indicates that at least a portion of the venoconstrictor response was mediated by reflex action. The increase in CVP began almost immediately in 11 of the 13 determinations made in 11 patients. This prompt rise in central venous pressure indicates a reflex rather than a humoral response, since distribution of a humoral agent, such as norepinephrine, by way of the circulation would probably require at least 10 seconds. It is entirely possible, however, that the prolonged elevation of central venous pressure in some of the patients may have been due to an added humoral effect.

TABLE III. MEASUREMENTS OF INCREASES IN CENTRAL VENOUS PRESSURE UNDER VARIOUS CONDITIONS REPORTED ELSEWHERE[2]

CONDITION	NUMBER OF SUBJECTS	NUMBER OF OBSERVATIONS	MEAN PRESSURE INCREASE (MM. Hg)
Post-Valsalva	9	28	2.6
Cold*	7	18	0.2
Exercise†	5	10	0.3
Hyperventilation	8	19	0.3
Tilt‡	8	13	1.6

*Immersion of feet and one hand in ice water.
†Alternate flexing and extending the knee and hip of one leg.
‡After 60° foot-down tilt of 4 minutes' duration.

It has been pointed out that reflex control of venomotor tone is important in over-all circulatory regulation. There are situations in which the normal circulatory system is called upon to make adjustments in accommodating to changes in blood volume or cardiac output. The reflex control of venomotor tone aids the circulatory system in making these adjustments.

In a normal person, such changes as a Valsalva maneuver or assuming the upright posture tend to reduce venous return to the heart and lower cardiac output. Widespread arteriolar constriction and increase in the peripheral arterial resistance will correct the resultant drop in blood pressure. The reflex venoconstriction which occurs increases venous return to the heart and helps to maintain the cardiac output.

The venoconstrictor mechanism has utility in circulatory disturbances in which the blood volume is decreased, such as in acute loss of blood from hemorrhage. In this case the increased venomotor tone helps to maintain cardiac out-

put. It would be disadvantageous, however, in conditions in which the blood volume is increased or in which the heart is incompetent in handling the venous return, as in congestive heart failure.[6]

The importance of reflex venoconstrictor responses is apparent in situations in which they are pathologically absent. In instances of paralysis of the autonomic nervous system by a disease process (i.e., diabetes, central nervous system disease), by sympathectomy, or by drugs, orthostatic hypotension is a complication. The basic defect in this condition is a lack of adequate arteriolar constriction in response to the lowered cardiac output upon assuming an upright posture; thus, the arterial pressure is not maintained. There are very large drops in cardiac output, however, which occur in some severe cases of the disorder. It has been suggested that loss of the reflex venoconstrictor response, and therefore a decreased venous return, could be responsible for the very large drops in cardiac output which occur in these severe cases.[9] This theory was later supported by data which showed absent, or markedly impaired, reflex contraction of venous segments in patients with postural hypotension due to autonomic nervous system disease.[2] This mechanism, then, has utility in counteracting circulatory changes which produce a lowered cardiac output, with or without change in blood volume.

The magnitude of the venoconstrictor response to autonomic stimulation by EST is indicative of the great degree to which this system can act to correct for circulatory changes.

SUMMARY

1. Central venous pressure was measured in 11 psychiatric patients during a period of electroshock and for several minutes afterward. Nine patients had electroshock for a duration of 5 seconds or less. Two patients were given electroshock on two different occasions for durations of 60 to 90 seconds.

2. Of the 9 patients who had electroshock for 5 seconds or less, 8 had increases in central venous pressure. The mean rise in central venous pressure was 5.4± 2.4 mm. Hg. The 2 patients who had electroshock for 60 to 90 seconds had increases in central venous pressure in all four instances. The mean increase in central venous pressure was 13.0± 3.1 in these 2 patients.

3. The time course of the rise in central venous pressure following stimulation of the autonomic nervous system by electroshock indicates that the rise in pressure is at least partially mediated by reflex action.

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Zones of Potential Interference, Dissociation, and Fusion: With Observations on the Contour of Retrograde P Waves

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The term "zone of potential interference" has been applied recently[1] to the period during which, if a subsidiary pacemaker becomes active and A-V dissociation results, the two coexisting impulses can meet and obliterate each other. It was suggested subsequently[2] that "zone of potential dissociation" was in two ways preferable: because it emphasized the result of the incoordination of the two impulses, dissociation, and because it avoided use of the ambiguous term, interference.

Interference began life as an admirable term; but because exponents of the arrhythmias have chosen to use it in differing and conflicting senses, the word has become a handmaid to confusion. Authorities such as Wilson, Mobitz, Katz, Pick, Langendorf, Winternitz, Barker, and others use the term in one sense, while others including Scherf, Bellet, Friedberg, Bain, Dressler, Ashman, Schott, Burchell, and others use it in an entirely different sense.* Without presuming to arbitrate, we may at least point to the absurdity of this situation and suggest that there should be a standard terminology by which everyone should abide. Until such time, in order to avoid confusion, one must always preface employment of the term by a statement of the sense in which it is used. The term "zone of potential interference" employs interference in the electrophysical sense (the interference of impulses rather than of rhythms[2]) and in our further discussion we shall continue to use it in this sense.

Further study of this zone of interference indicates that the suggested term, zone of potential dissociation, is not an entirely satisfactory substitute for zone of potential interference. This is because the zone of interference may be subdivided into an initial zone, wherein dissociation between atria and ventricles is total, and a terminal zone, in which the dissociation is only partial and atrial fusion beats result. These subsidiary zones may be called appropriately the zones of potential dissociation and fusion, respectively, and it is the purpose of this communication to illustrate this subdivision of the zone of interference. We believe that these concepts are of fundamental importance to a clear under-

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*For references see bibliography of Reference 2.

standing of the mechanisms of A-V dissociation, especially because it has been stated repeatedly that A-V dissociation can occur only when retrograde A-V block protects the atria from control by the faster beating lower center. That this is but a partial truth has become apparent.

It should be emphasized that these zones to be discussed are relative or potential rather than absolute; they exist only when the normal A-V relationship is disturbed and two pacemakers are in action, and they can be expressed only in terms of the timing of one pacemaker relative to the other.

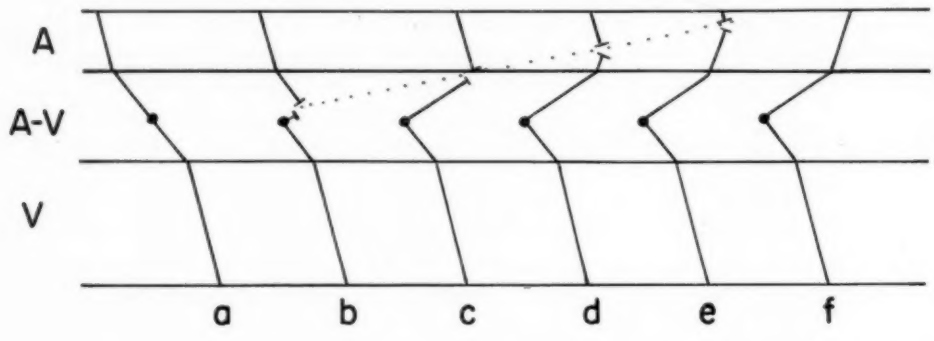

Fig. 1.—Diagram illustrating an idealized series of beats manifesting interference at progressively higher levels, during gradual transition from sinus to A-V nodal rhythm. A sinus beat (*a*) is followed by two beats showing A-V dissociation in which interference occurs in the A-V junctional tissues (*b,c*). The next two beats show atrial fusion at low (*d*) and high (*e*) atrial levels. The final beat is A-V nodal (*f*). The dotted line serves to draw attention to the upward progression of the site of interference.

Let us assume in Fig. 1 that two autonomous pacemakers are operative and that A-V conduction is unimpeded in both directions. Provided the atrial impulse arrives at the A-V node before it has discharged its impulse, a conducted beat results (*a*). If, however, the atrial impulse arrives just after the nodal impulse has been discharged, dissociation results (*b*). If the atrial impulse arrives later, dissociation will again result (*c*), unless it arrives so late that the ascending impulse already has entered the atrial muscle; in these circumstances dissociation is only partial and atrial fusion results (*d,e*). Finally, if the retrograde impulse reaches the S-A node before the sinus impulse has entered the atrial muscle, fusion no longer occurs, the atria are "captured" and A-V nodal rhythm prevails (*f*).

Instead of regarding the cycles in the diagram as isolated beats, they may be regarded as a series of consecutive beats illustrating the transition of sinus rhythm to A-V nodal rhythm in a functioning heart; such a sequence is shown in Fig. 2,*A*, illustrating a progressive upward shift of the site of interference with each succeeding beat. The opposite trend, namely, a downward shift of the site of interference, conversely occurs during transition from A-V nodal to sinus rhythm (Fig. 2,*B*).

One may assume that all or most hearts possess a potential retrograde A-V conduction time as well as a forward conduction time. Whenever circumstances conducive to A-V dissociation arise, its characteristics are influenced by the duration of forward and retrograde conduction times. If retrograde conduction is

impossible while forward conduction remains comparatively normal, the classical form of A-V dissociation with captured beats occurs—the P waves are able, as it were, to "overtake" and "pass" the QRS and subsequently effect ventricular capture. If, on the other hand, retrograde conduction is facile, there will be no captured beats and relatively short periods of dissociation will merge with runs of A-V nodal rhythm.

In other words, the duration of the opportunity for interference (and therefore dissociation) to occur is determined by the facility of the A-V tissues concerned for forward and retrograde conduction. If in a given heart forward conduction is normal and retrograde conduction, when it occurs, is rapid, so that the retrograde P wave is inscribed in front of the QRS complex (so-called "upper" nodal rhythm), the potential zone of interference is brief (Fig. 3,*A*); if forward conduction is normal but retrograde conduction is slower, so that the retrograde P wave is written following the QRS, the zone is obviously greater (Fig. 3,*B*); whereas, if forward conduction is prolonged and retrograde conduction is also markedly retarded, the zone will be maximal (Fig. 3,*C*).

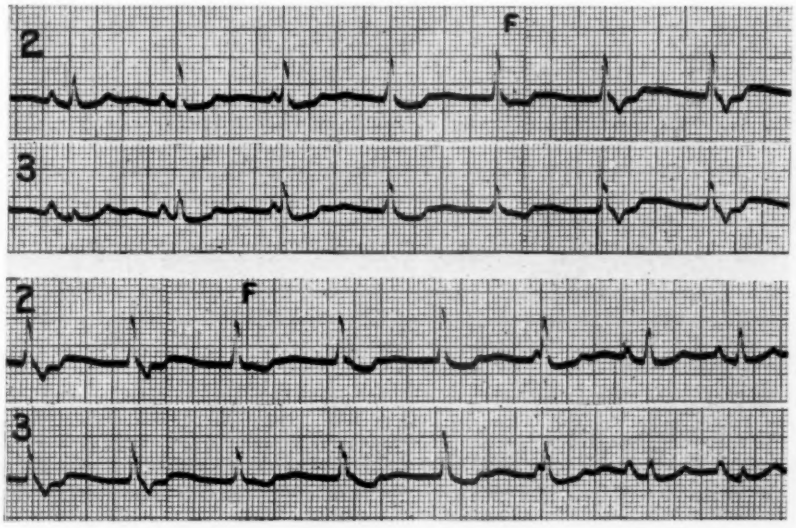

Fig. 2.—Two pairs of simultaneous strips. *A* **illustrates transition from sinus to A-V nodal rhythm via A-V dissociation and atrial fusion, whereas** *B* **illustrates the transition in reverse. In** *A*, **after one sinus beat, A-V dissociation develops "by default" because of sinus slowing; after three dissociated beats, atrial fusion (***F***) occurs and, in turn, is followed by two A-V nodal beats. In** *B*, **two nodal beats are followed by a fusion beat (***F***), three dissociated beats, and two sinus beats. In** *A* **the site of interference becomes progressively higher, and in** *B*, **progressively lower with successive beats. Because the fusion P wave in** *A* **is more negative than that in** *B*, **it presumably represents interference at a higher level than in** *B* **(i.e., Fig. 1,***e* **rather than 1,***d*).

It was pointed out above that the potential zones under discussion can be expressed only in terms of the timing of one pacemaker relative to the other. The zone of interference is perhaps most conveniently considered in terms of the period during which impulses must leave the S-A node in relation to the ascending or potentially ascending lower impulse, and thus it can be represented along the uppermost line of the diagrams in Fig. 3. The period of possible inter-

ference extends from just *after* the beginning of atrial activation by the S-A impulse (A) to just *before* the completion of potential or theoretic atrial activation by the retrograde impulse (C). Of this total zone of interference, the zone of dissociation extends to the last moment when an S-A impulse might leave the S-A node and effectively forestall the ascending A-V impulse from entering the atria (A-B), while the remainder of the total zone (B-C) is the zone of potential fusion. Thus, in electrocardiographic terms, the zone of potential interference extends from just *after* the beginning of the sinus P wave to just *before* the end of the potential retrograde P wave. Just as conveniently, and perhaps with more graphic appeal, these zones may be represented as shaded areas, as in Fig. 3, rather than mere linear measurements.

From the foregoing observations it will be apparent that the zone of fusion is relatively constant, whereas the zone of dissociation is greatly influenced by the rates of forward and retrograde conduction—the longer these conduction times, the longer the period of potential dissociation. If retrograde conduction is slow, the zone of fusion is a minor zone tacked on at the end of the zone of dissociation; whereas, if retrograde conduction is rapid, the zone of dissociation is curtailed and that of fusion may even exceed it in length (Figs. 3,*A* and 4).

CALCULATION OF ZONES

In order to calculate the approximate duration of these zones, four measurements are necessary: (1) the P-R interval, (2) the P′-R or R-P′ interval (whichever applies), (3) the width of the retrograde P (P′), and (4) the period required for the sinus impulse to reach the A-V junction. The first three of these can be measured from the electrocardiogram if both sinus and A-V nodal rhythms are present; and, according to Lewis,[3] in dogs it requires about 0.035 second from the start of atrial activation for the sinus impulse to enter the upper A-V junction. For the purposes of our argument, and in the absence of more exact information in human beings, we shall assume an interval of 0.03 to 0.04 second, although it well may be somewhat longer. Formulae may then be derived for the calculation of the various zones, as in Table I. It is obviously necessary to employ two sets of formulae, according to whether the retrograde P wave precedes or follows the QRS, because the R-P′ interval, being measured to the *beginning* of the P′ wave, does not include the duration of P′, whereas the P′-R interval obviously does.

If we apply these formulae to the tracings in Figs. 2 and 4, we arrive at the following results. In Fig. 2 the P-R interval is 0.16 second, the R-P′ interval

TABLE I

ZONE	IF P′ PRECEDES QRS	IF P′ FOLLOWS QRS
Interference	P-R − P′-R + duration P′	P-R + R-P′ + duration P′
Dissociation	P-R − P′-R − 0.03 to 0.04 sec.	P-R + R-P′ − 0.03 to 0.04 sec.
Fusion	duration P′ + 0.03 to 0.04 sec.	duration P′ + 0.03 to 0.04 sec.

is 0.10 second, and the P′ duration is 0.07 second. The zone of interference therefore totals 0.33 second, with that of dissociation totaling 0.22 or 0.23 second, and that of fusion totaling 0.10 or 0.11 second. In Fig. 4 the P-R interval is 0.11 second, the P′-R interval is 0.08 second, and the P′ duration is 0.07 second. In this case the three zones are, respectively, 0.10, 0.00, and 0.10 second. In other words, retrograde conduction is so rapid that the zones of interference and fusion virtually coincide; this means that the zone of dissociation is nonexistent, so that total dissociation (dissociation without fusion) cannot occur.

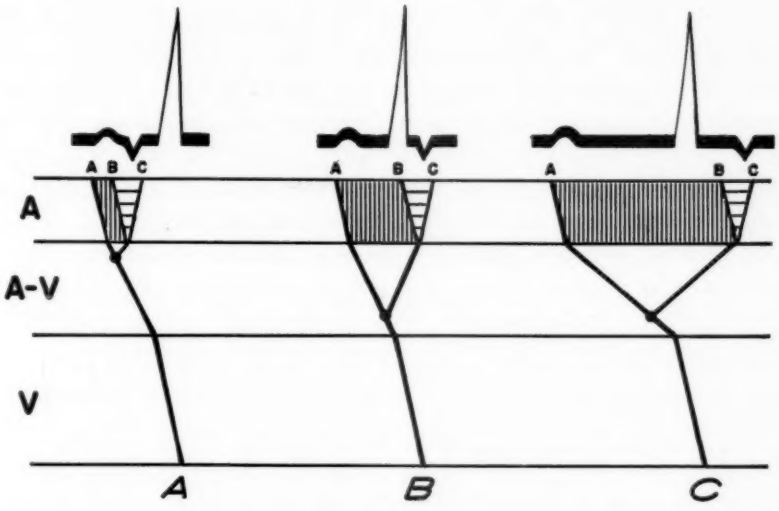

Fig. 3.—Forward and retrograde conduction are combined into an unreal but convenient synthesis. Both normal and retrograde Pwaves are shown in the "tracing" accompanying each diagram. The diagrams represent three hearts showing varying forward and retrograde conduction times. In each, A-C represents the zone of potential interference, A-B the zone of potential dissociation, and B-C the zone of potential fusion.

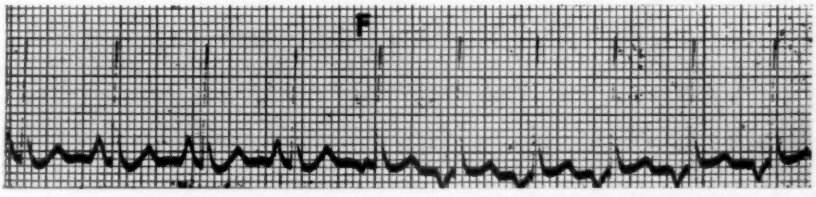

Fig. 4.—Tracing illustrating both S-A and A-V rhythms in sequence, with little difference between P-R (0.11 sec.) and P′-R (0.08 sec.) intervals. In such a heart, so long as similar conduction times obtain, A-V dissociation is barely if at all possible (cf. Fig. 3,*A*). See text for discussion.

THE CONTOUR OF RETROGRADE P WAVES

The foregoing observations prompt some consideration of the pattern of retrograde P waves. The inverted P′ is not a mirror-image of the normal sinus P wave; it is usually sharply pointed and narrower. From our observation of 26 cases with clearly measurable retrograde P waves, its width varies between 0.04 and 0.08 second, with a mean of 0.06 second. This contrasts with the more

rounded P wave of sinus origin whose width varies between 0.07 and 0.11 second. The normal rounded monophasic form of the sinus P wave is presumed generally to be due to tangential spread of activity through the atrial wall,[4] from right to left, whereby activation is completed earlier in the right than in the left atrium. In A-V nodal rhythm, on the other hand, the impulse spreads upward from the more centrally placed A-V junction and so produces more nearly simultaneous activation, and therefore quicker total depolarization, of the two atria.

Again, it has been our experience that the sinus P wave related to a ventricular premature beat is seldom seen on the upstroke of the T wave—it appears before or shortly after the QRS complex or is lost in it. This is in contrast with the situation in complete A-V block or A-V dissociation in which the P waves appear whenever they are due. Now, retrograde conduction in ventricular premature beats has been shown, particularly by means of esophageal leads, to be of common occurrence,[5] and the retrograde P waves that result tend to occur shortly before the point at which sinus P waves are expected. It is therefore tempting to assume that the observed absence of sinus P waves on the upstroke of the T wave is due to the presence of unseen (relatively isoelectric) fusion beats.

The duration of the zone of potential fusion was formularized above as equal to the duration of the P′ wave plus 0.03 to 0.04 second. It is thus by nature the most constant of the three zones, almost always measuring approximately 0.10 second (Fig. 3). If the R-P interval of a ventricular beat with retrograde conduction to the atria is measurable, the beginning of the zone of fusion can be inferred to be 0.03 to 0.04 second before the beginning of the P′ wave. The R-P interval of a ventricular premature beat is usually about 0.20 second[6]; therefore, the associated zone of fusion would start about 0.17 second after the beginning of the QRS and extend to about 0.26 second thereafter; generally, therefore, it would include the upstroke of the T wave. In other words, the upstroke of the T wave of the premature ventricular beat corresponds with the time when fusion between an antegrade sinus impulse and a retrograde ventricular impulse might be expected to occur.

SUMMARY

The development of A-V dissociation (interference-dissociation) is conditioned by the relative timing of atrial and ventricular pacemakers and is modified by the existing facility for both forward and retrograde conduction. The relationship that the discharge of one pacemaker bears to the discharge of the other may be expressed conveniently in terms of potential "zones"—particularly in terms of the timing of the atrial discharge relative to the discharge of the ventricular pacemaker.

For A-V dissociation to occur, the atrial discharge must take place during the "zone of potential interference." This zone, in turn, may be subdivided into an intitial "zone of dissociation" when interference takes place in the A-V tissues, and a terminal, rather constant, "zone of fusion" when interference takes place

within the atrial musculature and atrial fusion beats result. These potential zones are described in detail and illustrated.

Comment is made regarding the relative narrowness of retrograde P waves.

It is suggested that the frequently observed absence of sinus P waves on the upstroke of the T wave of ventricular premature beats may be explained by the occurrence of atrial fusion beats at that time.

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Applications of Electrokymography Based on a Comparison With Records From Dimensional Gauges In Situ

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The electrokymograph is the only continuously recording dimensional transducer in clinical use. Its principal application has been to record the patterns of dimensional changes of pathologic hearts and great vessels.[1-4] Certain pathologic conditions result in specific patterns. Recently, particular interest has centered around the use of the electrokymograph to differentiate stenosis from insufficiency in mitral valve disease.[5-7] The electrokymograph has also been used to some extent in the study of cardiovascular dynamics,[8-10] but does not permit quantitation of the dimensional changes. A quantitative electrokymographic circuit has been attempted,[11,12] but cardiovascular data obtained with these recording systems have not appeared.

Zinsser[13] and Morgan[11] have used electronic tests to evaluate electrokymographic equipment. In the present study the frequency response of the electrokymograph was determined in dynamic test situations. A more direct evaluation has been achieved by comparing electrokymograms recorded at specific sites with simultaneously recorded tracings from direct-measuring, dimensional transducers surgically installed in experimental animals. On the basis of these studies certain conclusions were drawn regarding the applications of electrokymography.

METHODS

Electrokymograms and records from direct-measuring transducers in the left ventricle, the aorta, and the vena cava in seven dogs were compared. The Cambridge electrokymograph was used in this study. The output signal from the filter amplifier unit was amplified by a Tectronix, type 122, low-level preamplifier, and was recorded on a Sanborn Poly-Viso. A 60-cycle, half-wave-rectified fluoroscope was used with the usual setting of 50 to 70 kilovolts and 2.5 milliamperes.

The nonlinearity of the output from the phototube as a border moves toward the ends of the light-sensitive slit has been cited in the past.[11-13] Special effort was made to record border

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motion in the central part of the phototube slit in order to minimize this difficulty. In a further attempt to counteract this limitation, a 1-cm. Lucite block was interposed between the fluorescent screen and the surface of the phototube according to the method of Morgan.[11]

The records from several dimensional transducers were used as standards for the evaluation of the electrokymogram. Appropriate gauges for use on the aorta, vena cava, and the left ventricle were selected, and surgically placed at specific sites on these structures. Subsequent electrokymograms were recorded from these same sites.

Left ventricular diameter was measured continuously by the sonocardiometer.[14] With this device the transit time of sound passing across the left ventricle was measured. The transmitter and receiver were barium titanate crystals sewn to the interventricular groove (see Figs. 1 and 2), so as to be diametrically opposed. One crystal was energized by bursts of high-frequency sound (3 megacycles per second) with a pulse duration of 1 microsecond. The transit time of these sound waves from one crystal to the other was calibrated in terms of linear diameter and recorded continuously on a Sanborn Poly-Viso.

Two types of variable-resistance length gauges were used to measure dimensional changes of the aorta. One of these gauges (Baldwin-Lima-Hamilton SR-4) consisted of foil-bonded, strain-sensitive wire wrapped around the aorta. This gauge was secured in such a way that changes in aortic circumference flexed the gauge, causing deformation of the strain-sensitive wire and producing variations in its electrical resistance. The other type, a mercury variable-resistance length gauge,[15,16] consisted of a mercury column conductor contained in thin-walled rubber tubing, which was also wrapped around the aorta. As the circumference of the aorta changed, this column lengthened and decreased in cross-sectional area, with the result that its electrical resistance also varied.

A modification of the mutual inductance method for measuring dimensional changes was used on the superior vena cava. This method was first developed by Perry and Hawthorne.[17] Irisawa[18] modified the method by adding a soft iron core to the coils. Two coils made of 200 turns of size 45 enameled copper wire wound about a soft iron core were sewn to the adventitia of the vena cava. One coil was activated by a 30-kilocycle alternating current, and the voltage variations induced in the secondary coil were rectified, amplified, and recorded on a Sanborn Poly-Viso. Such a gauge is sensitive, but nonlinear.

A Lead II electrocardiogram was used for timing the electrokymograms and the records from other transducers.

In many instances respiration was monitored by a pneumograph made up of flexible bellows fastened about the dog's thorax, elongation of the bellows activating a P23B Statham unbended strain gauge by compressing the contained air.

In all animals, recording was done from three to fourteen days after surgery. Necessarily, the dog was sedated with Pentothal and was therefore lying on the table during the recording period.

RESULTS

The frequency response characteristics of the electrokymographic system used in this study are shown in Fig. 1. A rotating wheel, which had three evenly spaced, identical lead spokes, was used for the dynamic determination of frequency response. With this device the amplitude of the electrokymographic deflections was found to fall off rapidly at frequencies of less than 1 cycle per second and was progressively attenuated between 7 and 30 cycles per second.

Performance of the electrokymograph at low frequencies was ascertained by determining its response to a square wave input (in this case a step function). By energization of a relay a lead plate was displaced suddenly from its position in front of the photocell. The step-function response obtained indicated a rise time of 0.02 second and an exponential decay despite a sustained input (Fig. 1).

The effects of respiration on the electrokymogram are also illustrated in

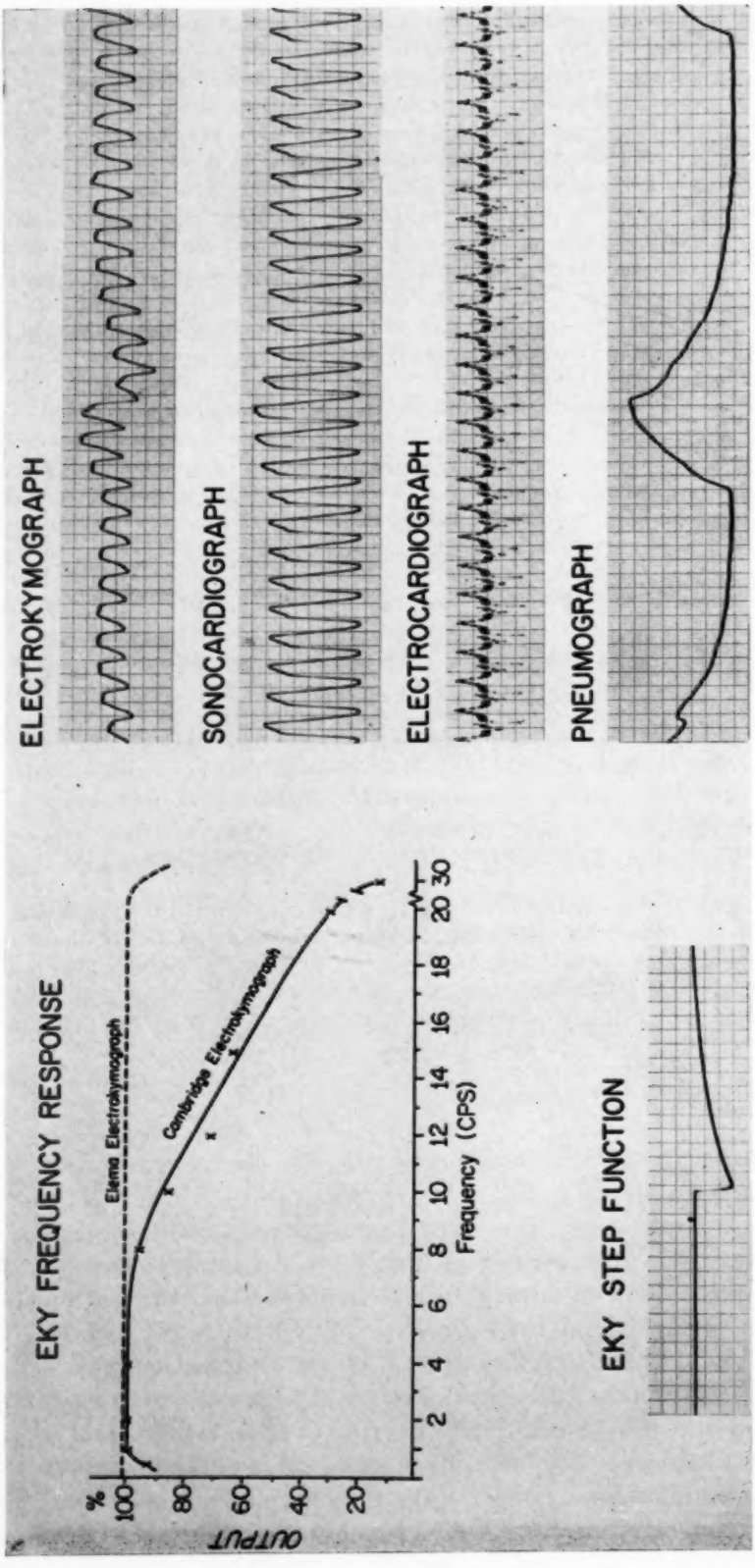

Fig. 1.—Left, frequency response characteristics of the Cambridge electrokymograph as they were found in test situations. Upper left is the response of this unit to an oscillation of constant amplitude and increasing frequency. Below is the response to a sudden displacement. Right, the effects of respiration on the left ventricular electrokymogram and the left ventricular sonocardiogram. The bellows pneumograph was used to measure respiratory chest excursions and an electrocardiograph was used to monitor the electrokymogram.

Fig. 1. In this instance, left ventricular border electrokymography (reflecting motion of the ventricular wall) was compared with left ventricular sonocardiometry (reflecting changes in left ventricular diameter), the record being monitored by electrocardiography and pneumography. During the rapid phases of respiration, inspiration, and early expiration, there is a fluctuation in the base line of the electrokymogram not shown by the sonocardiogram. This fluctuation results chiefly from a positional change of the heart secondary to motion of the diaphragm. Both records show an inspiratory increase in systolic excursion.

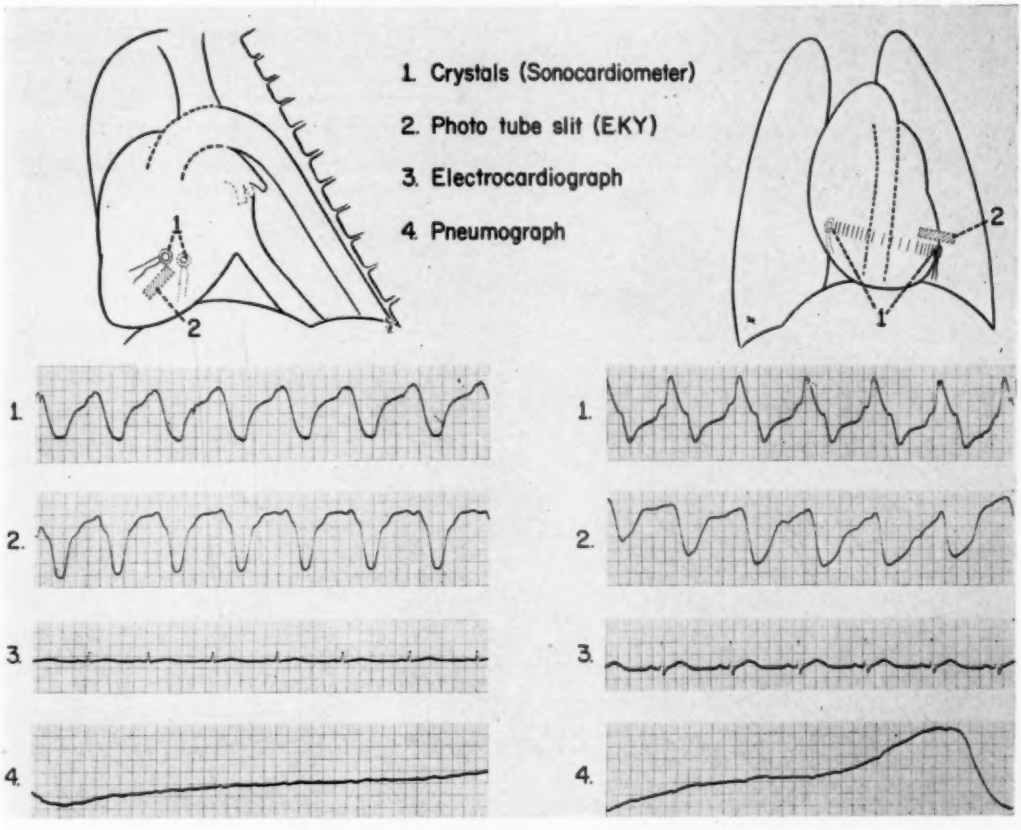

Fig. 2.—Left ventricular border and densographic electrokymograms are compared with the left ventricular sonocardiogram.

A comparison of the densographic and border-recording methods of electrokymography was made at several intrathoracic sites. The densographic method requires that the photomultiplier tube be centered within the borders of the fluoroscopic silhouette of the structure of interest, so that the only changes in radiodensity recorded are those caused by variations in the diameter of this structure. The border-recording method, on the other hand, involves placement of the phototube at right angles to the border of the structure's fluoroscopic silhouette, so that the tube senses motions of this border as it passes over the light-sensitive slit.

Such a comparison made for the left ventricle is shown in Fig. 2. It can be seen that good reproduction of the dimensional change can be obtained by either method, but that the densographic record provided a more consistent reproduction of the wave form inscribed by the sonocardiogram. In both electrokymographic records the timing of the major deflections conformed well with those of

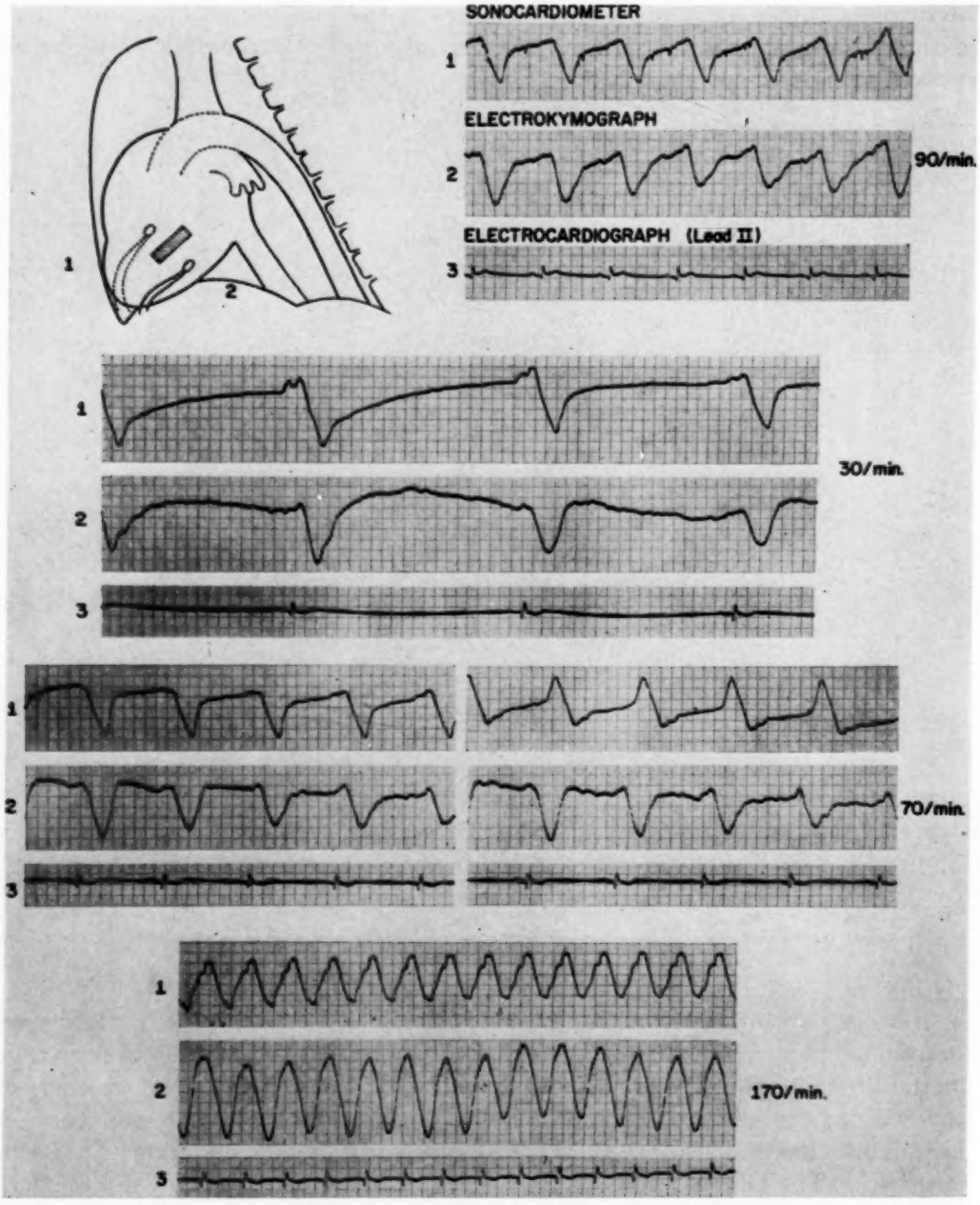

Fig. 3.—Left ventricular electrokymography and sonocardiometry are compared as the heart rate was varied from 30 to 170 per minute by means of right vagal and sympathetic nerve stimulation (i.e., an in vivo test of the electrokymograph's frequency characteristics).

dimensional gauge in situ. A similar comparison was made at two other sites, the superior vena cava and the descending aorta, with the same result, namely, that the record obtained by the densographic method was superior to that obtained by the border method.

With the densographic method of recording, left ventricular electrokymograms were recorded as the heart rate was varied by vagal stimulation. Again the criterion for evaluation of the electrokymogram was the sonocardiogram.

Electrokymograms most accurately reproduced the sonocardiograms at heart rates of 90 per minute. This finding is interpreted as being due to the fact that the change in ventricular diameter occurred at a frequency of 1.5 cycles per second, within the frequency range of 1 to 7 cycles per second of the Cambridge unit.

At a rate of 30 per minute, and to a lesser extent at 70 per minute, the electrokymogram differed from the sonocardiogram in that the ascending limb of the early diastolic filling phase displayed an overshoot with subsequent decay. Otherwise, the electrokymograms reproduced well the dimensional changes, including the higher frequency components associated with atrial systole and isometric ventricular contraction. These high-frequency components of the change in diameter were completely absent from the electrokymograms recorded when the heart rate was 170 per minute. On the basis of the sonocardiogram, these components had a frequency of 16 cycles per second, and were therefore roughly 30 per cent attenuated. Since they are of small magnitude, this attenuation would be enough to explain their absence from the electrokymograms recorded at this rapid heart rate.

Close perusal of the timing of the major deflections on the electrokymogram shows that although they lead those of the sonocardiograph by 0.03 second at a heart rate of 170 per minute, they lag by 0.03 second at heart rates of 30 per minute, a phase shift of 0.06 second.

DISCUSSION

The preceding records demonstrate that the electrokymograph can provide records that are good reproductions of the underlying dimensional changes as shown by the records from the dimensional transducers in situ.

The comparison of border and densographic electrokymography revealed that the densographic electrokymogram provided a better reproduction of the dimensional change as well as a more stable base line. The bases for this superiority in recording fidelity are that: (1) variations in radiodensity reflect the motion of both walls of the chamber being studied; and (2) having the phototube slit well within the silhouette of the chamber minimizes the effects of positional changes. As might be expected, variations in radiodensity, lacking the contrast provided by a border excursion, require greater amplification. Thus, the best electrokymograms were recorded from the left ventricle at heart rates of 70 to 120 per minute by means of the densographic technique.

The recording system used for this study might be referred to as a simple system, since more elaborate systems are available. The limitations of this system are not inherent in electrokymography, but rather are based on the limited frequency range of this system. One of these limitations is response attenuation

at frequencies of less than 1 and greater than 7 cycles per second, with a slight phase shift as the frequency increases over the range of 1 to 15 cycles per second. A second limitation is response decay at low frequencies and base-line wandering, both due to condenser discharge in the filter circuit of the electrokymograph.

These limitations in frequency response imposed by the Cambridge electrokymograph can be virtually eliminated by using an electrokymographic circuit of more elaborate design. Brief reference was made to the Elema electrokymograph,[19] which eliminates much of the electronic filtering present in the Cambridge unit by employing a balancing phototube on the fluoroscope side of the patient. Only differences in output of the recording phototube relative to that of the balancing phototube are recorded, so that the 60- or 120-cycle ripple of the fluoroscope is balanced out. In addition, the Elema circuit is DC-coupled, as opposed to the AC-coupled Cambridge circuit. These two factors (DC-coupling, and reduction in electronic filtering) are responsible for the Elema's flat response to frequencies of 0 to 15 cycles per second with the 60-cycle fluoroscope). With a 100-cycle fluoroscope the response is flat from 0 to 20 cycles per second, with 40 per cent attenuation at 30 cycles per second. The square wave response of this unit shows a rise time of 0.01 second and negligible decay in 0.3 second.

Nevertheless, there are limitations of electrokymography which should restrict its use to certain sites where these distorting factors are minimized or do not apply at all. Such distortions are the deflections superimposed by the motion of adjacent or overlying structures. The records most affected by such distortion were those from structures adjacent to the heart, the mediastinum and the diaphragm.

All distorting factors were exaggerated when the structure studied provided poor contrast in radiodensity or had a dimensional change of small amplitude. The electrokymogram required increased amplification in either case.

SUMMARY

1. In order to clarify the range of usefulness of electrokymography, electrokymograms obtained with a Cambridge instrument have been compared with records obtained by installing recording devices measuring directly the dimensional changes of the left ventricle, the aorta, and the vena cava in intact dogs. The response of the electrokymograph to mechanically produced oscillations with fixed amplitude and varied frequency, and to sudden sustained displacement, was also recorded.

2. With a simple electrokymographic recording system in which the design imposed certain frequency limitations, it was possible, nevertheless, to record accurately the dimensional changes reflected by in situ dimensional transducers.

3. It is emphasized that the distortions imposed by this simple recording system are largely the results of its limited frequency range (1 to 7 cycles per second) and of the type of filtering circuit employed. A more elaborate electrokymographic system, now commercially available, eliminates these distorting factors.

4. Finally, the little used densographic method of electrokymography was shown to be superior to border electrokymography in regard to reproduction of the actual dimensional change with minimal interference from positional change of the structure of interest.

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The Effects of "Dry" Heat on the Circulation of Man.
II. Splanchnic Hemodynamics

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In a previous communication[8] we presented the general hemodynamic data collected in 16 patients during an exposure for 2 hours to a relatively dry and warm environment of 98° F. ±1° and a humidity of 40 per cent ±3. The most important findings were significant decreases of the pulmonary and brachial artery pressures, systemic and total pulmonary vascular resistances, and the calculated left ventricular work, in the absence of a significant rise of the cardiac output.

The object of the present experiments was similarly to obtain data relevant to the hepatic venous outflow and the splanchnic vascular resistance. The control data were again obtained at the comfortable environment of 73° F. ±1° and a relative humidity of 40 per cent ±3. The subjects chosen for investigation had either normal hearts, or heart disease wherein the sole cause lay in factors burdening initially the left ventricle. None of the patients had liver disease or abnormal Bromsulphalein (BSP) retention.

MATERIALS AND METHODS

Thirty-four patients were investigated and divided into 4 groups: Group A was comprised of ten patients who had normal hearts or enlarged left ventricles. Determinations of splanchnic blood flow were carried out during a two-hour period in the comfortable environment only. These data served as the control determinations for the method. Group B was comprised of ten patients with normal hearts. Group C was comprised of seven patients with enlarged left ventricles, who were presumably compensated at rest, as arbitrarily determined by the recording of wedge pressures of less than 10 mm. Hg. Group D was comprised of seven patients with enlarged left ventricles, who were presumably in left ventricular failure at rest (wedge pressure greater than 12 mm. Hg).

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Following overnight and morning sedation (phenobarbital 0/032 and pentobarbital sodium 0/1) and an overnight fast, right-sided cardiac catheterization was performed employing a No. 6.5-8F Goodale birdseye catheter. The central venous pressures were obtained[8] and the catheter was then introduced into a right hepatic vein. A No. 19 intra-arterial needle was placed in the brachial artery of the catheterized arm for withdrawal of peripheral arterial blood samples, and recording of the arterial pressures. Brachial artery pressures were transduced via a P23A Statham strain gauge and recorded on a Brush oscillographic recorder. A 16 gauge cannula was introduced into a vein of the opposite arm for delivery of the BSP. After administration of a priming dose of 150 mg., the chemical was administered at a constant rate of 3 mg. per square meter of body surface per minute, according to the method of Bradley and associates.[2]

Following stabilization and attainment of a constant peripheral BSP level, the initial determinations of splanchnic flow were made. In the case of the patients in Groups B, C, and D, the room temperature was then elevated from 73° F. ±1° to 98° F. ±1° within 22 minutes, maintaining the humidity constant at 40 per cent ±3. Repeat determinations were made 1 and 2 hours following attainment of the high temperature.

In situations in which minor variations were noted in the peripheral concentrations of the BSP, adjustment was made with the proper correction, estimating the total plasma volume from the tables of Gibson and Evans.[5] Splanchnic blood flow was expressed in terms of cubic centimeters per square meter per minute (EHBFM²).

Samples of blood were drawn consecutively and in duplicate from the brachial artery and the hepatic vein for analysis of their spectrophotometrically[6] determined oxygen contents. Splanchnic oxygen consumption ($SMRO_2$) was calculated by the formula:

$$SMRO_2 = \frac{EHBFM^2 \times \text{A-V Difference}}{100}$$

and expressed in cubic centimeters per square meter per minute.

Splanchnic vascular resistance (SVR) was calculated according to the formula:

$$SVR = \frac{\text{Mean arterial blood pressure}}{EHBFM^2 \text{ in c.c./sec.}}$$

and expressed as millimeters of mercury per cubic centimeter per second per square meter.

The rate of blood flow in the finger was determined by the venous occlusion technique,[4] and rectal and skin temperatures were continuously observed, employing properly shielded iron constantan thermocouples, and recorded by a Brown potentiometer.

RESULTS

The individual data for Groups A, B, C, and D are presented in Tables I through IV, respectively. Averages, percentile changes, and significance analyses (Fisher's "t" test, groups less than 30) are presented in Table V.

The control subjects (Group A) showed no significant changes over a 2-hour period of observation in the brachial artery pressure, the brachial arterial-hepatic venous oxygen difference, the $EHBFM^2$, the $SMRO_2$, and the SVR.

The data for the patients in Groups B, C, and D showed significant decreases in the brachial artery pressure when compared to the data obtained in the comfortable environment, and to the pressures recorded for the control group.

There was an increase of borderline significance ($<.05>.02$) in the brachial arterial-hepatic venous oxygen difference in Groups B and C and no change in Group D. However, there was no significant difference between Groups B, C, and D and the control Group A.

TABLE I. INDIVIDUAL DATA FOR 10 SUBJECTS WITH NORMAL OR ENLARGED LEFT VENTRICLES IN WHOM ALL DETERMINATIONS WERE MADE AT 73°F. AND 40 PER CENT HUMIDITY

PATIENT	AGE	RACE, SEX	BODY SURFACE ($M.^2$)	DIAGNOSIS AND CARDIAC STATUS	C 1 2	P_{BA} (MM. Hg)	BA-HV AVD	EHBF	$SMRO_2$	SVR
E.S.	64	W, M	1.59	HCVD-LVH; no failure	C	188/110 (138)	4.50	1,029	46.2	8.0
					1	177/102 (125)	3.90	1,285	50.0	5.8
					2	175/100 (124)	3.97	1,136	45.0	6.6
A.P.	66	W, M	1.68	Bronchopneumonia, recovered; normal heart	C	138/83 (106)	5.09	742	37.8	8.6
					1	154/88 (115)	5.29	708	37.4	9.7
					2	151/83 (107)	5.35	695	37.2	9.2
T.T.	69	W, F	1.53	Acute pyelonephritis, recovered; normal heart	C	133/62 (88)	4.85	478	23.2	11.0
					1	140/68 (96)	4.76	473	22.5	12.0
					2	136/64 (90)	4.58	494	22.6	11.0
T.W.	30	N, M	1.71	Bronchopneumonia, recovered; normal heart	C	92/55 (71)	4.97	733	36.0	5.8
					1	92/53 (67)	5.42	796	43.1	5.2
					2	100/56 (74)	5.68	731	41.0	6.0
G.S.	71	W, M	1.61	Cerebral thrombosis; normal heart	C	103/46 (71)	5.51	572	31.5	7.4
					1	124/51 (80)	5.39	620	33.4	8.8
					2	124/49 (80)	5.78	552	32.0	8.7

C.N.	65	W, M	1.69	Syphilitic aortic insufficiency; LVH and D., borderline failure (wedge pressure 12 mm. Hg)	C	167/28	(72)	6.71	923	62.0	4.7
					1	171/28	(73)	7.52	749	56.0	5.8
					2	179/30	(76)	6.68	720	48.0	6.3
M.H.	71	W, M	1.63	Bronchiogenic carcinoma. Coronary disease; no enlargement	C	159/61	(95)	5.87	927	54.4	6.1
					1	166/65	(98)	6.30	838	52.8	7.0
					2	156/58	(90)	6.09	714	43.5	7.6
J.S.	71	W, M	1.64	Bronchopneumonia, recovered; normal heart	C	151/54	(87)	4.03	875	35.3	6.0
					1	164/58	(99)	4.71	807	38.0	7.3
					2	156/54	(95)	4.00	769	30.8	7.4
J.M.	43	N, M	1.78	Delirium tremens, recovered; normal heart and liver function	C	118/73	(90)	4.58	702	32.2	7.7
					1	114/70	(87)	4.51	800	36.1	6.5
					2	116/71	(88)	3.92	812	31.8	6.5
W.A.	66	W, M	1.80	Aortic stenosis and insufficiency; LVH and D., failure left (wedge pressure 14 mm. Hg)	C	163/53	(100)	4.73	997	47.2	6.0
					1	176/61	(109)	4.70	786	36.9	8.3
					2	185/64	(115)	4.98	980	48.8	7.1

P_{BA} = Brachial artery pressure; the mean pressure is given in parentheses. BA-HV AVD = Brachial artery-hepatic venous oxygen difference in volumes per cent. EHBF = Estimated hepatic blood flow in c.c./M.²/min. $SMRO_2$ = Splanchnic oxygen consumption in c.c./M.²/min. SVR = Splanchnic vascular resistance in mm. Hg/c.c./sec./M.². C, 1, and 2 = Determinations obtained initially and at the end of 1 and 2 hours, respectively. (These abbreviations will be used in all subsequent tables.)

TABLE II. INDIVIDUAL DETERMINATIONS FOR 10 SUBJECTS WITH NORMAL HEARTS

PATIENT	AGE	RACE, SEX	BODY SURFACE ($M.^2$)	DIAGNOSIS AND CARDIAC STATUS	C* 1 2	P_{BA} (MM. Hg)	BA-HV AVD	EHBF	$SMRO_2$	SVR
O.S.	35	N, M	1.66	Bronchopneumonia, recovered	C	111/70 (87)	5.65	819	46.3	6.4
					1	111/73 (85)	5.76	714	41.1	7.1
					2	78/52 (59)	6.73	671	45.1	5.3
C.K.	37	N, M	1.95	Bronchopneumonia, recovered	C	132/87 (105)	5.55	737	40.9	8.5
					1	115/78 (94)	5.75	670	38.5	8.4
					2	96/62 (75)	5.92	565	33.4	8.0
A.W.	53	N, M	1.73	Bronchopneumonia, recovered	C	104/56 (72)	4.64	808	37.5	5.3
					1	88/52 (63)	5.46	792	43.2	4.8
					2	70/44 (52)	5.17	660	34.1	4.7
F.W.	30	W, M	1.58	Bronchopneumonia, recovered	C	120/75 (89)	4.70	792	37.2	6.8
					1	98/65 (76)	5.20	842	43.8	5.4
					2	71/48 (55)	5.64	1,003	56.6	3.2
O.J.	51	N, M	1.67	Bronchopneumonia, recovered	C	112/52 (72)	4.97	405	20.1	10.7
					1	110/55 (73)	5.42	535	29.0	8.2
					2	103/49 (65)	5.68	490	27.8	7.9

J.S.	42	W, M	1.76	Delirium tremens, recovered; normal liver function	C	128/61 (83)	7.23	912	65.9	5.4
					1	88/43 (60)	5.92	1,390	82.3	2.6
					2	71/35 (50)	5.82	1,057	61.5	2.8
S.S.	54	N, M	1.65	Undiagnosed infiltration, RUL; afebrile	C	157/92 (113)	4.40	758	33.4	8.9
					1	123/72 (92)	4.40	786	34.6	7.0
					2	109/67 (71)	4.76	830	39.5	5.1
M.W.	49	W, M	1.77	Alcoholic neuropathy; normal liver function	C	137/82 (100)	5.13	842	43.2	7.1
					1	111/76 (88)	6.94	702	48.7	7.5
					2	100/70 (80)	7.22	711	51.3	6.8
G.B.	62	W, M	1.60	Angina pectoris; no cardiac enlargement	C	144/80 (111)	8.50	497	42.2	13.4
					1	125/80 (96)	9.17	447	41.0	12.8
					2	105/70 (85)	9.29	376	34.9	13.5
C.W.	46	W, M	1.87	Delirium tremens, recovered; normal liver function	C	152/88 (117)	5.14	999	51.3	7.0
					1	134/83 (104)	7.53	978	73.6	6.4
					2	136/83 (107)	8.09	994	80.9	6.4

***Initial determinations (C) obtained at 73° F. and 40 per cent humidity; experimental (1 and 2) after 1 and 2 hours' exposure to 98° F. and 40 per cent humidity.**

TABLE III. INDIVIDUAL DETERMINATIONS FOR 7 SUBJECTS WITH ENLARGED LEFT VENTRICLES AND NORMAL WEDGE PRESSURES (PROCEDURE AS FOR SUBJECTS IN TABLE II)

PATIENT	AGE	RACE, SEX	BODY SURFACE ($M.^2$)	DIAGNOSIS AND CARDIAC STATUS	C 1 2	P_{BA} (MM. Hg)	BA-HV AVD	EHBF	$SMRO_2$	SVR
L.B.	23	N, M	2.01	Rheumatic aortic insufficiency; no history of failure	C	99/40 (64)	4.41	475	20.9	8.1
					1	92/43 (62)	3.84	700	26.9	5.3
					2	70/35 (49)	3.74	1,073	40.1	2.8
A.M.	72	W, M	1.85	Antecedent hypertension; recovered. Cerebral thrombosis; treated failure	C	148/94 (114)	4.22	1,035	43.7	6.7
					1	118/78 (88)	5.42	1,004	54.0	5.3
					2	105/73 (85)	5.00	996	50.0	5.1
S.J.	62	N, F	1.55	Labile hypertension; treated failure	C	132/82 (98)	6.90	671	46.3	8.7
					1	104/61 (76)	7.75	572	44.3	8.0
					2	86/52 (62)	9.95	488	48.6	7.7
B.H.	36	W, F	1.51	Hypertensive cardiovascular disease, no history of failure	C	180/113 (133)	5.03	697	35.0	11.5
					1	148/90 (114)	6.75	726	49.0	9.4
					2	153/94 (115)	6.65	739	49.1	9.3
A.S.	56	W, M	1.79	Hypertensive cardiovascular disease, no history of failure. Remote CVA	C	239/117 (160)	3.84	856	32.9	11.3
					1	203/104 (133)	4.64	1,051	48.8	7.6
					2	181/94 (126)	4.67	711	33.2	10.6
L.S.	44	W, F	1.61	Antecedent hypertension; recovery from failure	C	158/91 (122)	7.40	500	37.0	14.7
					1	146/91 (119)	6.47	449	29.0	15.9
					2	111/67 (89)	7.90	456	36.0	11.7
J.B.	75	W, M	1.99	Hypertensive cardiovascular disease; angina pectoris. No history of failure	C	225/103 (153)	5.60	505	28.3	18.2
					1	184/75 (113)	9.06	317	28.7	21.3
					2	179/65 (103)	6.96	428	29.8	14.5

TABLE IV. INDIVIDUAL DETERMINATIONS FOR 7 SUBJECTS WITH ENLARGED LEFT VENTRICLES AND ELEVATED WEDGE PRESSURES (PROCEDURE AS FOR SUBJECTS IN TABLES II AND III)

PATIENT	AGE	RACE, SEX	BODY SURFACE ($M.^2$)	DIAGNOSIS AND CARDIAC STATUS	C 1 2	P_{BA} (MM. Hg)	BA-HV AVD	EHBF	$SMRO_2$	SVR
C.R.	48	W, M	1.81	Rheumatic aortic insufficiency and stenosis	C	135/44 (78)	6.62	411	27.2	11.4
					1	141/50 (82)	7.13	467	33.3	10.6
					2	115/42 (69)	6.94	613	42.5	6.8
W.H.	30	N, M	1.92	Left ventricular hypertrophy and dilatation of unknown cause	C	93/68 (76)	5.26	738	38.8	6.2
					1	93/68 (76)	—	678	—	6.7
					2	90/64 (71)	4.04	664	26.8	6.4
C.S.	44	N, M	1.75	Rheumatic aortic insufficiency	C	176/96 (113)	6.27	799	50.1	8.5
					1	150/83 (103)	8.87	840	74.5	7.3
					2	152/84 (104)	8.22	763	62.7	8.2
B.G.	52	N, M	1.47	Antecedent hypertension	C	115/90 (99)	12.12	462	56.0	12.9
					1	93/72 (80)	10.72	472	50.6	10.2
					2	75/58 (67)	10.25	471	48.3	8.5
B.S.	65	W, F	1.75	Hypertensive cardiovascular disease	C	244/109 (164)	6.64	1,015	67.4	9.7
					1	235/103 (157)	6.20	994	61.6	9.4
					2	188/82 (132)	6.78	959	65.0	8.3
T.J.	39	W, M	1.92	Hypertensive cardiorenal disease (BUN = 38 mg. %)	C	186/118 (154)	4.98	769	38.3	12.1
					1	165/95 (127)	5.97	716	42.7	10.7
					2	158/90 (123)	4.97	783	38.9	9.4
W.J.	49	N, M	1.82	Syphilitic aortic insufficiency	C	149/54 (88)	5.10	527	26.9	10.0
					1	132/49 (79)	6.93	509	35.3	9.3
					2	132/53 (80)	7.01	587	41.1	8.2

TABLE V. AVERAGES, PERCENTILE CHANGES, AND SIGNIFICANCE ANALYSES FOR THE FOUR GROUPS

		MEAN P_{BA} (MM. Hg)	BA-HV AVD	EHBF	$SMRO_2$	SVR
A. Controls	C	92	5.08	798	40.6	7.1
	1	95 + 3.3%	5.25 + 3.3%	786 − 0.1%	40.6 0%	7.6 + 7.0%
	2	94 + 3.2%	5.10 + 0.3%	760 − 4.8%	38.1 − 6.1%	7.6 + 7.0%
	P (c vs 2)	<.5 >.4	<.9 >.8	<.4 >.3	<.3 >.2	<.2 >.1
B. Normal Heart, Heat	C	95	5.59	757	41.8	7.9
	1	83 − 12.6%	6.15 + 10.0%	786 + 3.8%	47.6 + 13.9%	7.0 − 11.4%
	2	70 − 26.3%	6.43 + 15.0%	736 − 2.8%	46.5 + 11.2%	6.4 − 19.0%
	P (c vs 2)	<.001	<.05 >.02	<.7 >.6	<.3 >.2	<.01 >.005
C. Enlarged Left Ventricle, Normal Wedge Pressure, Heat	C	120	5.34	677	34.9	11.3
	1	101 − 15.8%	6.27 + 17.4%	688 + 1.6%	41.5 + 19.0%	10.4 − 8.0%
	2	90 − 25.0%	6.41 + 20.0%	698 + 3.1%	41.0 + 17.5%	8.8 − 22.1%
	P (c vs 2)	<.001	<.05 >.02	<.9 >.8	<.1 >.05	<.01 >.005
D. Enlarged Left Ventricle, Elevated Wedge Pressure, Heat	C	110	6.71	674	43.5	10.1
	1	100 − 9.1%	7.64 + 13.9%	668 − 0.9%	49.7 + 14.2%	9.2 − 8.9%
	2	92 − 16.4%	6.89 + 0.3%	691 + 2.5%	46.5 + 7.0%	8.0 − 20.8%
	P (c vs 2)	<.01 >.005	<.8 >.7	<.7 >.6	<.5 >.4	<.02 >.01

Significance Analyses of Control Group A Versus Groups B, C, and D. The Comparisons Are Between the Final Percentile Changes in Group A Versus Those in the Other Groups. (*Fisher's "t" test, groups less than 30*)

P (Controls vs B)	<.001	<.2 >.1	<.9 >.8	<.3 >.2	<.02 >.01
P (Controls vs C)	<.001	<.3 >.2	<.7 >.6	<.3 >.2	<.02 >.01
P (Controls vs D)	<.02 >.01	<.9 >.8	<.6 >.5	<.6 >.5	<.02 >.01

The EHBFM[2] and $SMRO_2$ showed no significant changes in any of the experimental groups, and no difference when compared to the control Group A.

There were no significant differences in the changes in the aforementioned parameters among Groups B, C, and D when the latter were compared to each other. This analysis is omitted from Table V.

The flow of blood in the finger increased significantly in all patients exposed to the warm environment. All these patients also showed slight but significant increases in the rectal temperature, averaging 1.4° F. at the end of 2 hours. These data were virtually identical to those previously reported[8] and have been omitted from the tables.

The clinical observations were again as previously reported,[8] with a minimum of restlessness in a few patients, and the occasional development of Cheyne-Stokes respiration associated with elevation of the room temperature in those patients with enlarged left ventricles.

DISCUSSION

It had been stated by Bazett[1] that an increase in the ambient temperature would of necessity cause a decrease in the splanchnic blood flow and an increase in splanchnic vascular resistance. This statement was based on a previously reported investigation by Rein.[7] The latter author, employing a thermostromuhr, measured the changes in blood flow in the exposed superior mesenteric vein of the dog. The anesthetized animal was isolated in an enclosed chamber and exposed to sudden changes of temperature in the environment by alternately blowing in cold and hot air. It was stated that cold air caused an increase in flow, and that warm air produced an abnormally low flow. The latter observations were not supported by recorded data.

Although not documented, it is possible that a decrease in splanchnic blood flow and an increase in splanchnic vascular resistance may occur when the cardiac output in man is made to increase significantly by exposure to an excessively high temperature and humidity.[3] This is not the case in a situation in which a resting and horizontally placed individual is not restless, and attention is paid to the prevention of a significant disparity between increased body metabolism and heat dissipation.

The finding of a decrease in the splanchnic vascular resistance with no change in the splanchnic blood flow matches the physiologic directions of our previously reported experiments, wherein we noted no significant increase in the cardiac output, coupled with significant decreases in the systemic and total pulmonary vascular resistances.

SUMMARY

Ten patients with normal hearts, 7 with enlarged left ventricles not in failure, and 7 with enlarged left ventricles in failure were subjected for 2 hours to an ambient temperature of 98° F. ±1° and a comfortable relative humidity of 40 per cent ±3. Ten additional control patients, who were studied only in a comfortable environment of 73° F. ±1° and a relative humidity of 40 per cent ±3, showed no significant changes in the various parameters which were measured.

Exposure to the warm environment caused a significant decrease in the brachial artery pressure and in the splanchnic vascular resistance. There was no significant change in the estimated hepatic blood flow and in the calculated splanchnic oxygen consumption.

The responses to heat were similar in the patients with normal hearts and in those with enlarged hearts, regardless of the state of compensation of the left ventricle.

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Direct Recording of Heart Sounds and Murmurs From the Epicardial Surface of the Exposed Human Heart

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Phonocardiography has been proved to be a very useful tool in cardiac diagnosis. Although by this method a good knowledge of acoustic phenomena of the heart has been achieved in the last twenty years, many problems still await solution. Thus, technical improvements in recording and filtration systems have been devised recently for a more nearly correct analysis of heart sounds and murmurs. A better approach to some clinical problems seems to be via intracardiac and direct epicardial phonocardiography. While the first method has been developed fully by several authors, the second, which was employed as early as 1917, by Wiggers and Dean,[1] has since been applied only in animals.[2-4] The opening of the epicardial sac, as is usually done during heart surgery in man, has offered us an opportunity for the application of the second method in human beings.

This study was planned with the hope that by recording the heart sounds and murmurs directly from the epicardial surface of the various chambers of the heart, valuable information could be obtained about the transmission and diffusion of acoustic phenomena and the site of origin of still ill-defined murmurs. Some partial results have been published already elsewhere.[5,6]

METHOD AND MATERIAL

A suitable transmission system which could be easily sterilized was adopted. A glass funnel (1 cm. in diameter) which could be kept adherent to the surface of the heart by the surgeon's hand was connected to the microphone by a polyvinyl tubing, 45 cm. long, whose size (internal bore 0.6 cm. in diameter) was selected in accordance with the recommendations of Rappaport and Sprague.[7,8] The transmission characteristics of the whole system were tested against the vibrations of various frequency ranges (40 to 400 cycles per second) produced by a calibrated sound generator. A moderate loss of amplitude, but no gross distortion of the vibrations was noted. This can be shown even by standard phonocardiograms (Fig. 1).

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The Sanborn Twin-Beam phonocardiograph was used as the recording equipment; the paper speed was always 75 mm. per second. A simultaneous electrocardiogram was taken for timing purposes.

Seventy-five patients were studied: 30 of the patients had pure mitral stenosis; 10 had mitral stenosis plus insufficiency; 5 had mitral stenosis plus tricuspid insufficiency; 5 had aortic valvular stenosis; 7 had pulmonic valvular stenosis; 12 had atrial septal defect; and 6 had patent ductus arteriosus.

Fig. 1.—Phonocardiograms recorded over the apex: *A*, with the microphone applied directly on the chest; *B*, with the tubing connecting the glass funnel to the microphone.

Before surgery a standard phonocardiogram was recorded in all patients on the clinical areas of auscultation, so that a comparison between the epicardial and precordial tracings would be possible. However, in such a comparison one has to take into account the modifications of the heart sounds induced by thoracotomy and anesthesia. As far as the absolute intensity is concerned, in general, at the surface of the heart the cardiac sounds are from 5 to 20 times louder than over the precordium.

RESULTS AND COMMENT

Mitral Stenosis.—Forty-five patients were studied; they ranged in age from 18 to 44 years. In 30 of them there was no clinical evidence of other valvular lesions; in 10 there was some degree of mitral insufficiency; in 5 there was an associated tricuspid insufficiency. The patients of the first group showed a

typical precordial phonocardiogram, consisting of: (1) loud, snapping first sound, (2) loud, sometimes split second sound, (3) diastolic rumble, best recorded over the apex, followed by a "crescendo" presystolic murmur, when the sinus rhythm was maintained, and (4) opening snap of the mitral valve, widely recorded over the mid-precordium and pulmonic area. A moderate to loud systolic murmur over the apex and axilla was present in the patients of the second group. A blowing systolic murmur over the sternal area, increasing with deep inspiration, was recorded in the patients of the third group.

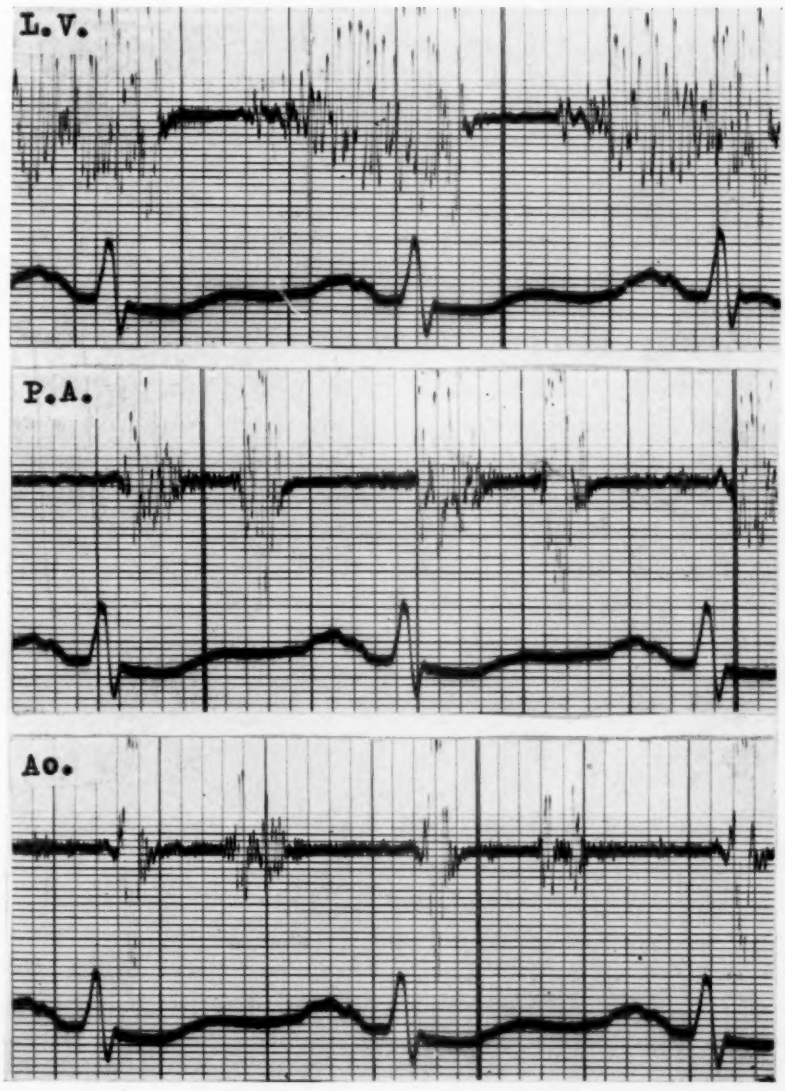

Fig. 2.—Case of pure mitral stenosis. The tracings were recorded over the left ventricle, the pulmonary artery, and the aorta (from above). Note the large diastolic vibrations over the left ventricle. The beginning of the first sound is not clearly visible. A short early systolic murmur (ejection murmur) is present over the pulmonary artery, where the second sound is prolonged and very loud. Over the aorta the second sound is split.

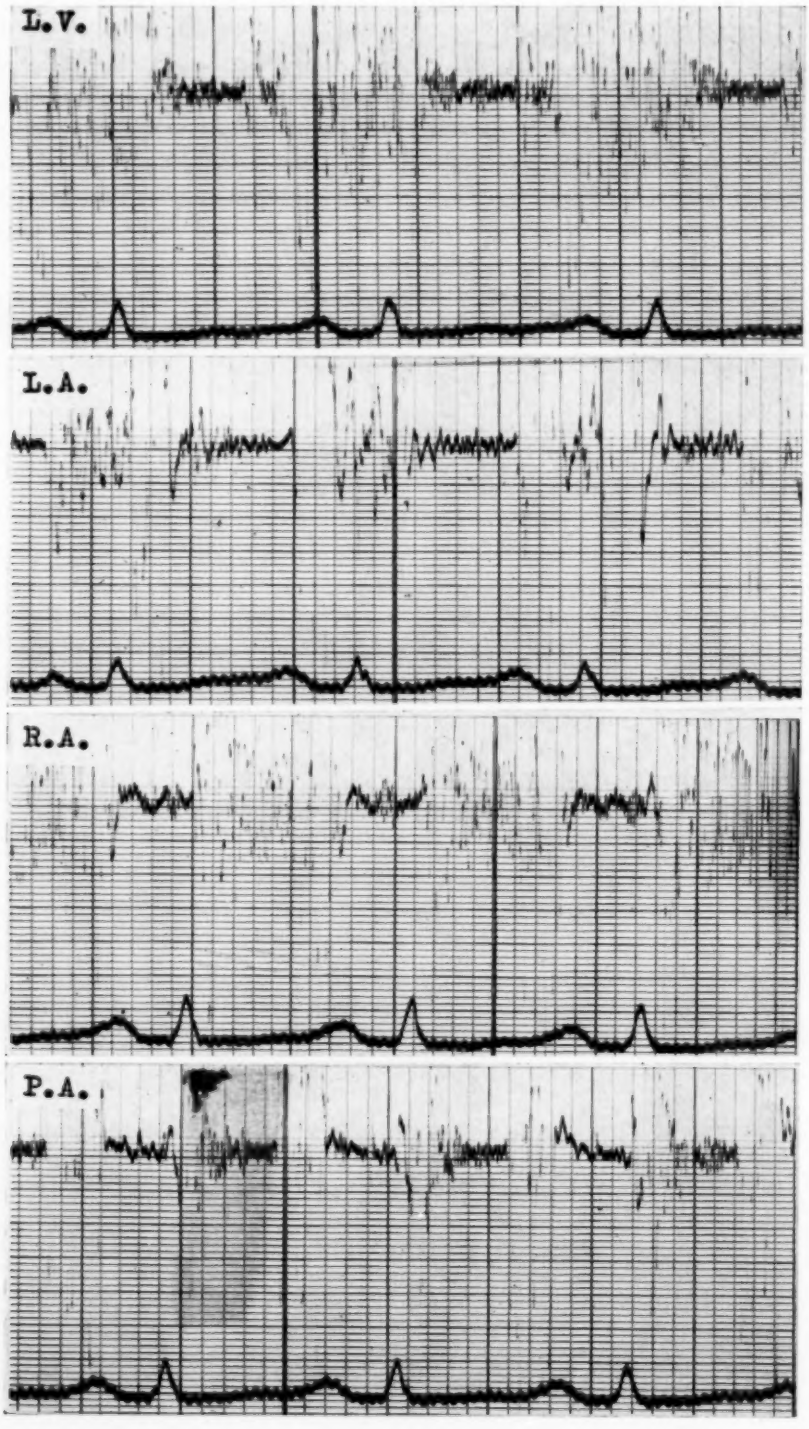

Fig. 3.—Case of mitral stenosis plus tricuspid insufficiency. The tracings were recorded over the left ventricle, the left atrium, the right atrium, and the pulmonary artery (from above). Over the left ventricle the diastolic vibrations are larger than those of the first sound. Over the right atrium a very loud systolic murmur of tricuspid regurgitation is recorded. A short ejection early systolic murmur is present over the pulmonary artery.

During surgery, before mitral commissurotomy was performed, the following points on the surface of the heart were explored: (1) left wall of the left ventricle, (2) anterior wall of the left ventricle, near the A-V groove, (3) anterior wall of the left atrium, and (4) anterior wall of the pulmonary artery, just above the semilunar valve.

The first sound was louder over the surface of the left ventricle than anywhere else. The second sound was loudest over the pulmonary artery; however, it was well recorded over the left atrium and ventricle. In some cases with split second sound, the aorta also could be reached with the exploring funnel. No difference between the aortic and pulmonic components over the two great vessels could be ascertained so that a criterion for their identification could be inferred. The opening snap of the mitral valve had its greatest intensity over the left atrium; however, in many instances it could be recorded with the same amplitude over the pulmonary artery. In most cases the vibrations of the diastolic rumble over the left ventricular wall were equal or even larger than the first sound (Fig. 2). This never happened in the precordial tracings. A possible explanation is that the lower pitched vibrations of the rumble are filtered out by the tissues of the chest wall.

In the cases of associated valvular incompetence, a loud systolic murmur was constantly recorded over the left atrium; in some of them the murmur had the greatest intensity mostly over the posterior aspect of the left atrium. This could be due to the direction of the regurgitant flow and would explain the diffusion toward the axilla and the back of the apical systolic murmur of mitral insufficiency.

When tricuspid insufficiency was present, a systolic murmur was recorded similarly over the right atrium (Fig. 3).

In some cases of tight mitral stenosis, with enlarged pulmonary artery, a very loud systolic murmur was recorded over this vessel; the murmur sometimes spread over the left atrium and the aorta.

It should be emphasized that many times the sounds and even the murmurs which originate in a definite site of the heart are clearly recorded over another structure which does not have any direct functional connection with the site of origin. For instance, the second sound is usually well transmitted to the left atrium, and the opening snap of the mitral valve to the pulmonary artery. As a matter of fact, both arterial trunks strictly contact the atrial wall. This shows that inside the heart itself the diffusion of sounds can occur not only by way of the blood stream, but also by anatomic contiguity.

Comparing the epicardial with the precordial phonocardiograms, we found that a good similarity exists between the left ventricular and the apical tracings, on the one hand, and between the pulmonary arterial tracing and the tracing recorded over the left intercostal space, on the other hand. No other consistent correspondence could be demonstrated between the precordial and free heart wall tracings.

Pulmonic and Aortic Valvular Stenosis.—In the 7 cases of pulmonic valvular stenosis, a diamond-shaped loud systolic murmur was always recorded over the trunk and the right pulmonary artery. This may be due to contiguity, as stated

above. In comparison with the tracings recorded over the trunk, those recorded distally along the right pulmonary artery show a progressively later appearance of the systolic murmur, which ultimately overlaps the second sound. This is possibly due to the fact that the second sound is transmitted along the vascular wall at the sound speed in a fluid milieu, while the murmur, continuously originated by a persistent turbulent flow distally from the stenotic valve, travels at a lower speed, which approximates that of the pulse wave.[9] A similar pattern was observed in the 5 cases of aortic valvular stenosis (Fig. 4).

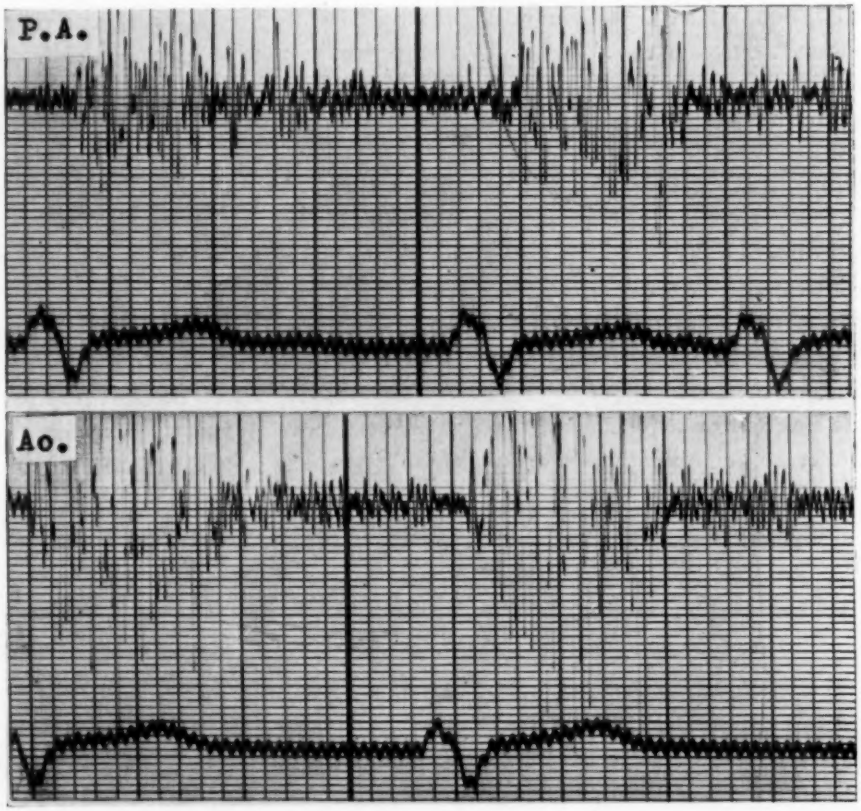

Fig. 4.—Case of aortic valvular stenosis and insufficiency. The tracings were recorded over the pulmonary artery and the aorta. Note the diamond-shaped systolic murmur and the "decrescendo" early diastolic murmur over the aorta. The same pattern is present, with lower intensity, over the pulmonary artery.

Atrial Septal Defect.—Direct phonocardiograms have been recorded in 12 cases of patency of the foramen ovale. In none of them was there pulmonary hypertension nor clinical evidence of pulmonary or tricuspid insufficiency. During surgery, before the defect was closed, the following points of the heart surface were explored: (1) the lateral wall of the right ventricle, (2) the anterior wall of the right atrium, (3) the anterior wall of the pulmonary trunk, (4) the right branch of the pulmonary artery, and (5) the wall of the pulmonary veins entering the left atrium.

In all cases, conventional precordial phonocardiograms had shown: (1) a loud, harsh systolic murmur in the second and third intercostal spaces along the left sternal edge, (2) a prolonged, split second sound, and (3) low-pitched, low-amplitude diastolic vibrations, best recorded in the third and fourth intercostal spaces at the mid-sternal line. In the literature, there is no complete agreement about the origin of the last murmur. Some authors have attributed

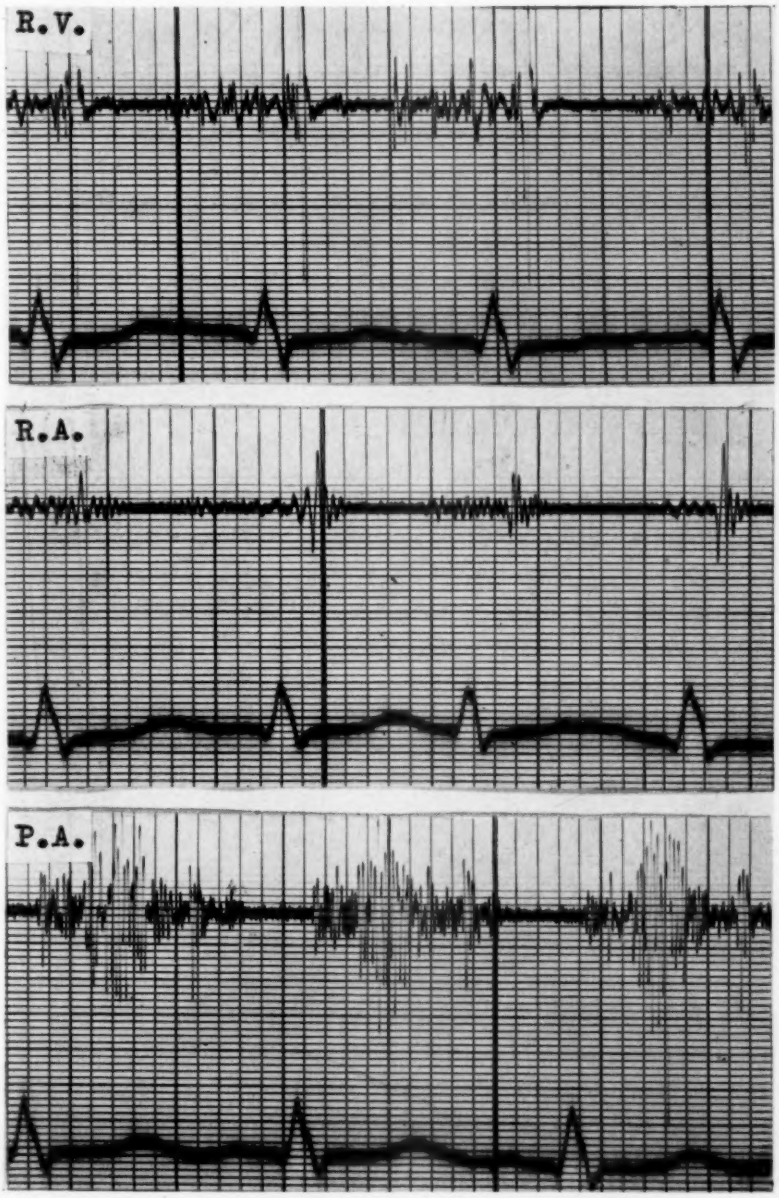

Fig. 5.—Case of atrial septal defect. The tracings were recorded over the right ventricle, the right atrium, and the pulmonary artery (from above). Note that the diastolic rumble is of much higher amplitude over the ventricle than over the atrium. A loud diamond-shaped systolic murmur is present over the pulmonic trunk.

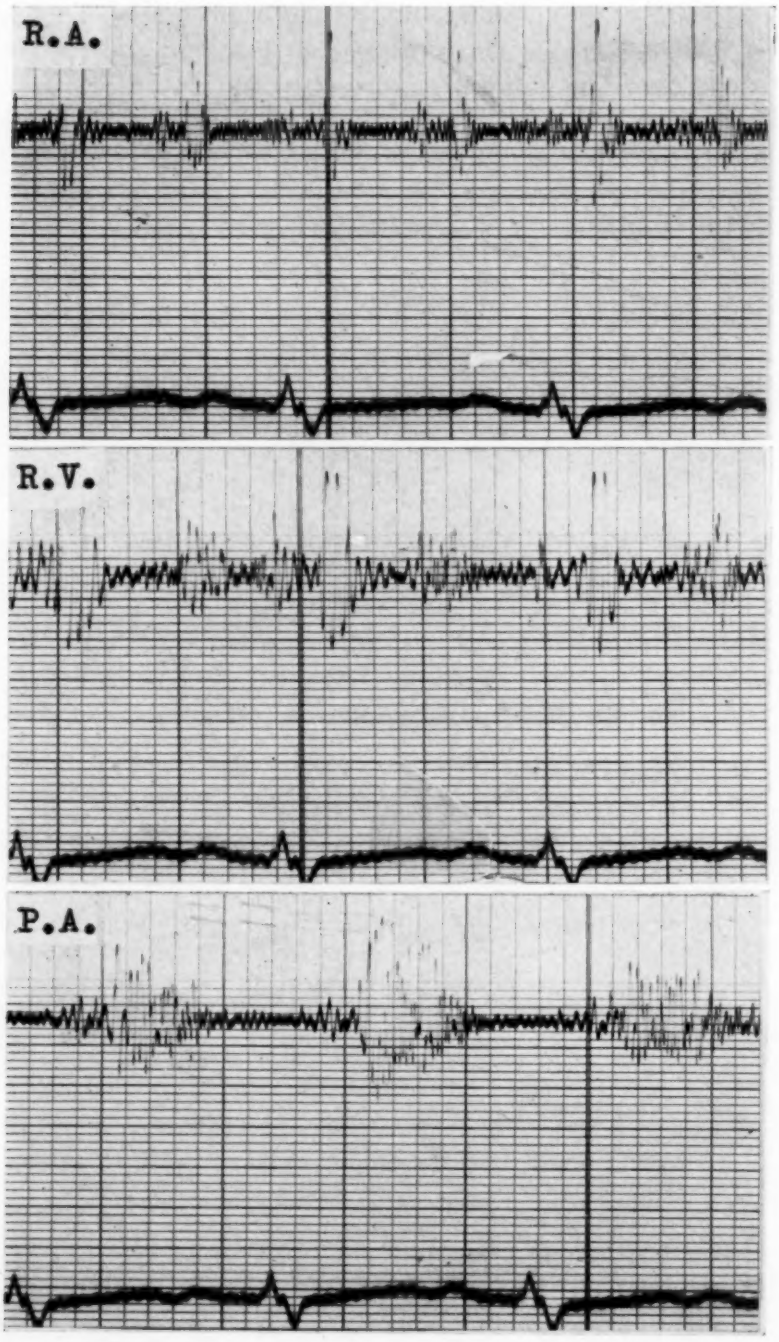

Fig. 6.—Case of atrial septal defect. The tracings were recorded over the right atrium, the right ventricle, and the right pulmonary artery (from above). Over the right pulmonary artery, note the late appearance of the diamond-shaped systolic murmur, which overlaps the second sound.

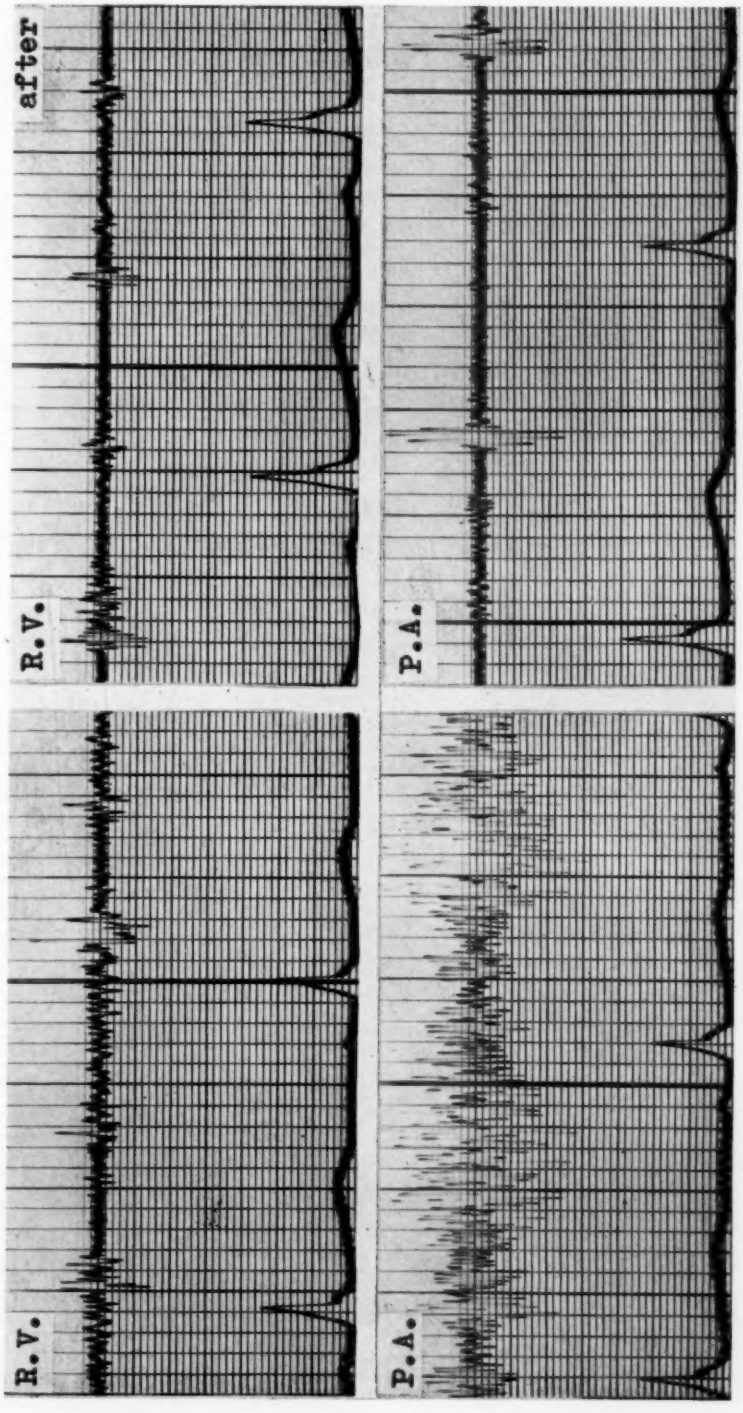

Fig. 7.—Case of patent ductus arteriosus. The tracings were recorded over the right ventricle and pulmonary artery, before (left) and after (right) the surgical closure. It is evident that both the diastolic vibrations over the right ventricle and the continuous machinery murmur have disappeared after the surgical closure. Only a faint systolic murmur is present over the pulmonary artery.

it to the passage of blood through the septal defect; however, most of them believe that the murmur is due to the eddies produced by the increased flow through the tricuspid valve, and indeed, it is often louder at the time of rapid ventricular filling. Low-pitched continuous vibrations created when the blood flows in the pulmonary veins (venous hum) do not seem, to us, to be clearly identifiable by phonocardiographic recordings or by auscultation.

The epicardial phonocardiograms have quite a different shape, depending on the zone explored. Over the right atrium and ventricle both the first and the second heart sounds were large and well identifiable. Over the same chambers the low-pitched diastolic vibrations appeared in those cases in which they were present also in the precordial tracings. An accurate study of the timing of the diastolic rumble has not been possible because of the cardiac rate, but it was always louder over the right ventricle (Fig. 5). This could be assumed to indicate that it originates in the ventricular cavity. In none of our cases was it possible to record continuous low-pitched vibrations (venous hum) over the pulmonary veins.

The very faint systolic vibrations over the right atrium and ventricle and over the aorta seem to be transmitted from the pulmonary artery, where a very loud diamond-shaped systolic murmur was recorded with the greatest intensity. This observation gives clear-cut proof that the systolic murmur of atrial septal defect originates in the pulmonary artery. It is interesting to observe that over the right pulmonary artery, at some distance from the semilunar valves, the systolic murmur shows a definite delay, as has been already described in the cases of pulmonary stenosis (Fig. 6).

Patent Ductus Arteriosus.—Direct epicardial phonocardiograms recorded in 6 cases of noncomplicated patent ductus arteriosus, without severe pulmonary hypertension, gave the following results: (1) The continuous "machinery" murmur was present, with greatest intensity over the pulmonary artery, at the same level or slightly below the opening of the ductus. A similar murmur of much lower intensity could be recorded over the aorta. (2) Low-pitched diastolic vibrations were observed over both ventricles, mostly over the right. This can be attributed to a relative tricuspid stenosis, due to the dilatation of the right chambers of the heart.

Important changes were observed after the surgical closure of the ductus arteriosus: the continuous murmur disappeared completely, while a short and faint mid-systolic murmur was still present over the pulmonary artery. This murmur is likely to be produced by the persistent dilatation of the latter vessel. The diastolic rumble over the right ventricle was no longer recorded (Fig. 7).

SUMMARY AND CONCLUSIONS

Direct epicardial phonocardiography was performed in a series of 75 selected patients who underwent cardiac surgery. Some tentative conclusions can be drawn: (1) The absolute intensity of heart sounds and murmurs over the cardiac surface is 5 to 20 times greater than over the precordium. (2) Low-pitched vibrations are likely to be filtered out by the tissues of the thoracic wall. (3) The

transmission of sounds and murmurs inside the heart itself and probably over the precordium takes places not only by way of the blood stream, but also by a topographical contiguity of different structures. (4) The site of origin of some controversial murmurs, such as the pulmonic systolic murmur in atrial septal defect and the functional nature of the diastolic rumble in several conditions, including left-to-right shunts, could be ascertained.

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Factors Involved in Digitalis Sensitivity in Chronic Pulmonary Insufficiency

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The role of digitalis in the therapy of chronic cor pulmonale has stimulated considerable controversy. White,[1] in 1934, stated that the drug was often helpful in this condition, while Friedberg,[2] in 1950, claimed that it is usually not beneficial. Ferrer and her co-workers,[3] in 1950, reported on the hemodynamic effects of intravenous digoxin in chronic cor pulmonale. When congestive failure was present there was a moderate rise in cardiac output and a slight but significant rise in pulmonary artery pressure. The right ventricular end-diastolic pressure decreased. After a period of combined therapy directed toward the underlying pulmonary disease, as well as digoxin, there was subsidence of cardiac failure, a return of the cardiac output to normal, and restoration of pulmonary artery and right ventricular pressures to near-normal levels.

Gray and others,[4] using intravenous lanatoside C, elicited increased cardiac output and pulmonary artery pressures in patients with chronic pulmonary disease. However, some of their cases exhibited increased right atrial mean pressure and right ventricular end-diastolic pressure. Arterial oxygen declined in some instances. Impaired ventilatory function occurred in other cases.

In a previous communication, the present authors[5] described frequent sensitivity to digitalis in patients with chronic cor pulmonale manifesting severe hypoxia and hypercapnia. Lown and Levine[6] emphasized the relationship of the therapeutic and toxic effects of digitalis to the concentration of potassium in the myocardial cell. Anoxia, edema, acidosis, and prolonged exercise are known to cause cellular depletion of potassium.[7-10]

Previous studies performed in the authors' laboratory, using radioisotope dilution techniques, indicated significant depletion of body potassium, retention of body sodium, and expansion of the extracellular (radiosodium) space in patients with chronic pulmonary insufficiency.[11]

With this background, a study of possible factors relating to digitalis sensitivity in chronic pulmonary insufficiency was carried out.

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METHODS

Twenty-nine subjects with chronic pulmonary insufficiency were studied. Measurements of total body exchangeable potassium (TBK) and sodium (TBNa) were performed by a method described by one of the present authors.[12] Coincident with the final collection of blood for those measurements an arterial blood sample was collected under basal conditions. Measurements of arterial blood gases and pH were carried out by standard techniques.[13-15] Immediately after the collection of arterial blood, 1.2 mg. of acetyl strophanthidin was injected intravenously and the electrocardiogram was monitored continuously for 30 minutes. None of these patients had been receiving digitalis previously.

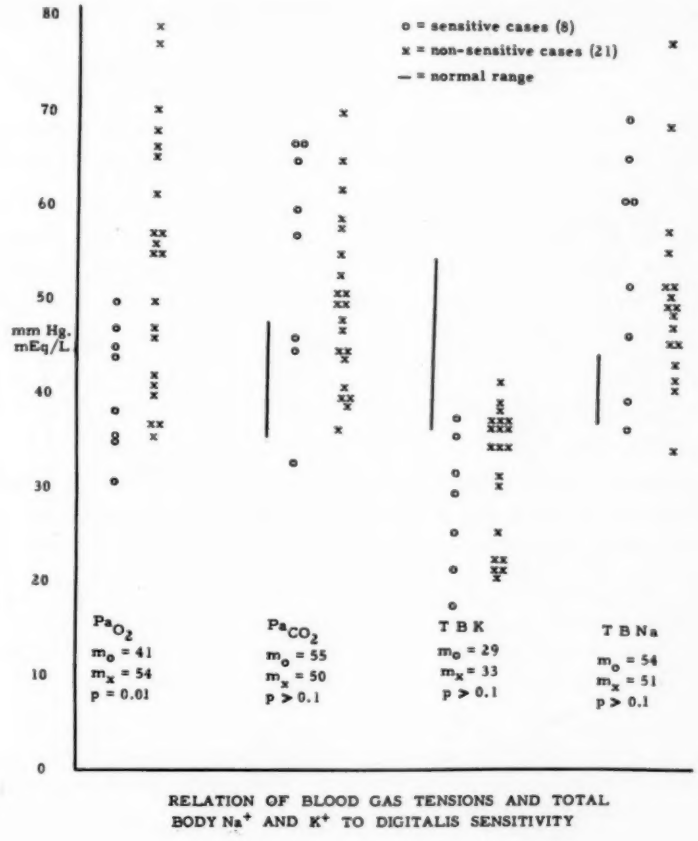

Fig. 1.—Distribution of calculated arterial oxygen and carbon dioxide tensions, total body potassium, and total body sodium in 8 subjects exhibiting sensitivity to acetyl strophanthidin and in 21 without sensitivity.

RESULTS

Chronic obstructive pulmonary emphysema was present in 28 subjects. The remaining patient was proved to have chronic interstitial pulmonary fibrosis by lung biopsy, and eventually, by postmortem examination.

Of these, 8 exhibited electrocardiographic evidences of sensitivity, such as transient atrioventricular dissociation, increased atrioventricular conduction time, and ventricular premature contractions. These manifestations were noted

as early as 4 minutes after injection of acetyl strophanthidin and subsided within a period of 20 minutes. No evidences of sensitivity were found in the other 21 patients.

The mean calculated arterial oxygen (Pa_{O_2}) for the sensitive patients (41 mm. Hg) was significantly lower than that for the nonsensitive patients (54 mm. Hg) ($p = 0.01$) (Fig. 1). The mean TBK was lower for the sensitive group than for the nonsensitive group, whereas the mean TBNa and calculated arterial carbon-dioxide tension (Pa_{CO_2}) were higher for the sensitive group (Fig. 1). However, none of these latter differences between the sensitive group and the nonsensitive group were statistically significant at the 10 per cent level ($p > 0.1$).

COMMENT

Although significant alterations in total body exchangeable sodium and potassium are present in patients with chronic pulmonary insufficiency, these factors appear to be poorly correlated with the presence or absence of digitalis sensitivity in the patients studied.

This study indicates that sensitivity to digitalis in chronic pulmonary insufficiency is more apt to occur in the presence of severe hypoxia. Therefore, digitalization should be employed with caution in the presence of the more severe grades of hypoxia.

SUMMARY

Of 29 patients with chronic pulmonary insufficiency, 8 exhibited electrocardiographic evidences of sensitivity to acetyl strophanthidin. The degree of arterial hypoxia was significantly lower in the sensitive group.

The authors are indebted to Catherine Osgood, B.A., Ruth Scheer, B.S., and Albert Johnson, Sc.B., for their technical assistance, and to Iris Kiem, M.S., M.P.H., for her invaluable analyses.

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Postoperative Myxedema Cardiopathy: An Unusual Instance Which Developed in the Immediate Postoperative Period. Case Report and Review of the Literature

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The nature of the enlarged cardiac silhouette occasionally encountered in patients with myxedema has been the subject of controversy since Zondek[1] first reported the cardiac manifestations of myxedema. Kern and associates[2] believe that pericardial effusion is a constant and early major manifestation of myxedema, and that the enlargement of the cardiac silhouette is due primarily to fluid in the pericardial sac. Hamilton and Greenwood[3] noted cardiac hypertrophy and persistence of mucoid material in the heart muscle of a patient treated for myxedema who succumbed to other causes. These authors point out the fact that no proof of the reversibility of these changes has been demonstrated. They imply a significant myocardial factor is operative in myxedema. Ellis and associates[4] have demonstrated by hemodynamic studies that although no uniform cardiovascular response occurs in myxedema, there is diminished cardiac output, with no change in any of the gradients. They explain this finding on the basis of "compensatory adjustment to lowered oxygen consumption." They conclude that the cardiac manifestations of myxedema are due to involvement of the entire myocardium, and the abnormal physiology is unrelated to pericardial effusion. Studies of myocardial metabolism in myxedema are not readily available. The report of Scheinberg and associates[5] indicates that the changes in myxedema are secondary to a "generalized reduction in organ blood flow," and probably related to imparied oxygen and glucose metabolism. It is conceivable that, as in beriberi,[6,7] the changes in the heart in myxedema are not always reversible with specific therapy. The high incidence of coronary artery disease in the age group in which myxedema usually occurs is an additional factor to consider. Perhaps, until the question of what causes the enlarged cardiac silhouette can be definitely resolved, the views of White[8] seem logical. He states that three factors are probably responsible in most cases: (1) dilatation, (2) increase in "bulk of heart muscle" (possibly due to interstitial edema), and (3) pericardial effusion.

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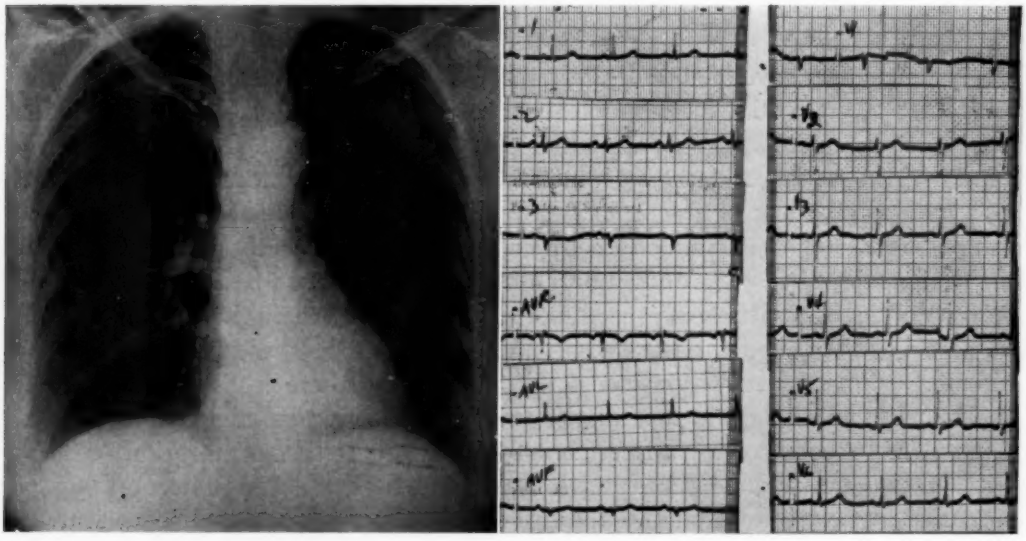
Enlargement of the cardiac silhouette in myxedema is, for the most part, unattended by signs of congestive heart failure. Physical examination, routine chest x-ray, or the electrocardiogram usually provide the first clue. It would appear from the literature that the onset is insidious and cryptic. The following case report is of interest in that evidence of an enlarged cardiac silhouette was detected approximately 10 days following thyroidectomy in an apparently euthyroid patient.

CASE REPORT

A 54-year-old white woman was admitted to the Veterans Administration Hospital for the first time in November, 1956, with the chief complaint of swelling in the anterior portion of her neck. The patient stated that to the best of her knowledge she had first noted her neck swelling approximately 1 year prior to admission. The swelling tended to increase slowly, and she had been more aware of it in the past 2 or 3 months. Some pressure and slight difficulty in swallowing were noted. The patient was examined elsewhere in August, 1956, at which time it was noted



A. *B.*

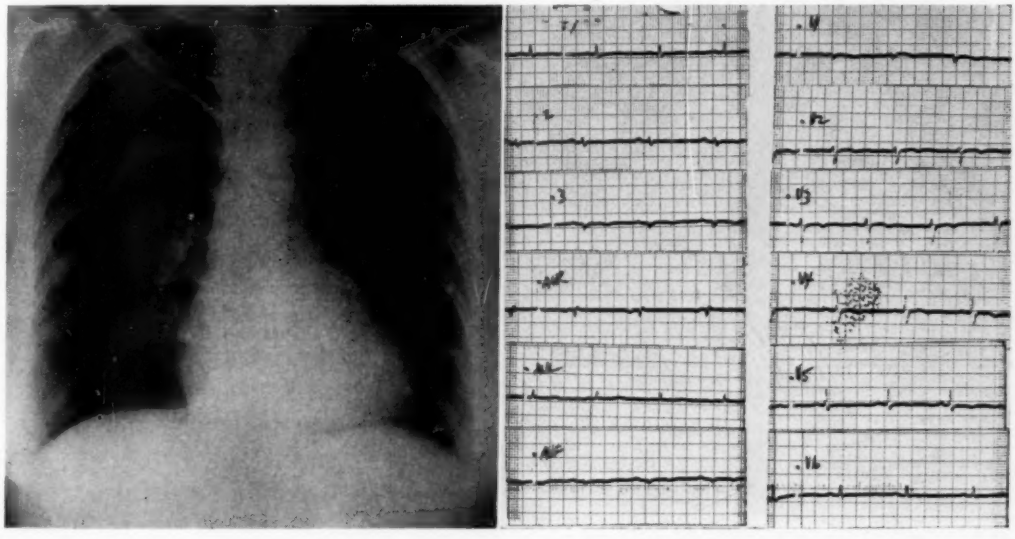
Fig. 1.—*A*, Posteroanterior x-ray of the chest preoperatively. *B*, Preoperative electrocardiogram.

that she had a questionably enlarged thyroid isthmus. There were no nodules noted. Routine blood count, urinalysis, and chest x-ray were within normal limits. The protein-bound iodine was 4.1 mcg. per cent. She was placed on one grain of thyroid daily for 2 weeks, and then two grains daily. Following this therapy for approximately 1 month, there was no objective evidence of change in size of the gland. She was re-examined elsewhere in October, 1956, with complaints of discomfort in the neck. Examination revealed questionable nodules in the thyroid. There were no voice changes or dysphagia noted. The protein-bound iodine was 7.2 mcg. per cent, and a 24-hour iodine uptake study was 8.1 per cent (normal 15 to 35 per cent). On admission to this hospital the patient denied any loss of weight or obvious gain in weight. She was not aware of any voice changes. She did complain of some nervousness and of frequent "hot flashes." She denied any history regarding skin changes or difficulty in management of her hair. There was no history of palpitation, flushing, aerophagia, or rapid heart action. The patient had been in excellent health all of her life, and she had been in military service from 1944 to 1945. It was also revealed that the patient had consulted an osteopath and had been given a prescription for

pills which contained homeopathic doses of iron, iodine, and copper. She stated that she took these pills during April, 1956, for approximately 3 weeks and then discontinued them of her own volition. She had had some menopausal complaints which had been present for 3 years, but which were controlled with injections of estrogen.

Physical examination on admission to the hospital revealed a well-developed, well-nourished white woman who did not appear to be acutely or chronically ill. Blood pressure was 130/88 mm. Hg. The significant positive physical findings revealed that the thyroid gland was enlarged, particularly in the isthmus and left lateral lobe; the latter appeared to be somewhat nodular and firm, but no definite fixation to the underlying tissues could be determined. There were no palpable lymph nodes. The remainder of the physical examination was entirely within normal limits.

Laboratory examinations showed the following: W.B.C. was 10,050 with 53 per cent neutrophils, 34 per cent lymphocytes, 7 per cent monocytes, 4 per cent eosinophils, and 1 per cent basophils; hemoglobin was 15.0 Gm.; hematocrit was 44 per cent. Urinalysis was within normal limits. VDRL was nonreactive. On Nov. 20, 1956, two microcuries of radioiodine were given: the percentage uptake at 6 hours was 3.2 per cent; at 24 hours it was 1.1 per cent. (Normal range of uptake at 6 hours is 5 to 25 per cent; normal range of uptake at 24 hours is 10 to 36 per cent.) Serum calcium was 10.6 mg. per cent. Total protein was 6.9 Gm., albumin 4.9 Gm., globulin 1.9 Gm. Urea nitrogen was 24 mg. per cent.



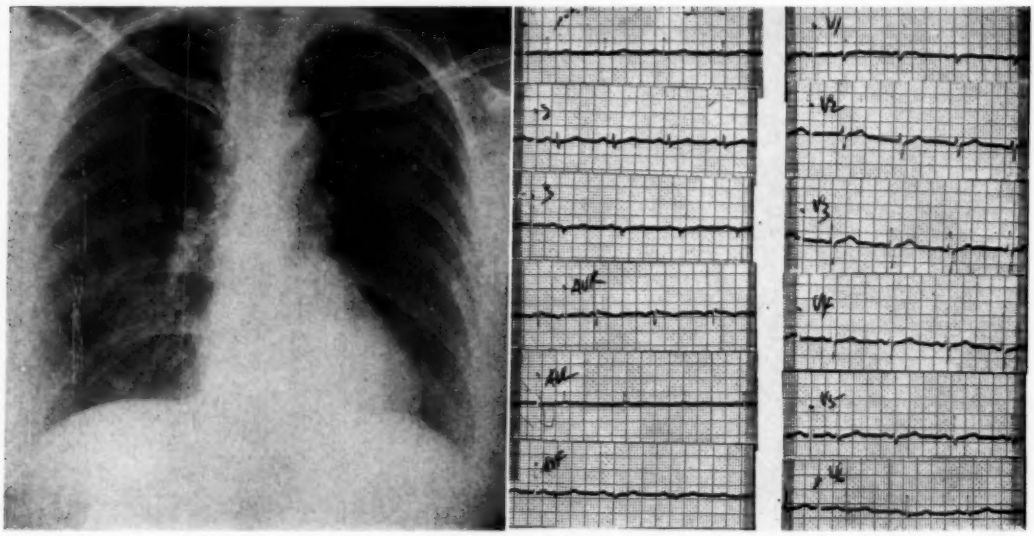
A. *B.*

Fig. 2.—*A*, Posteroanterior x-ray of the chest about 2 weeks postoperatively. Note the globular cardiac silhouette. *B*, Electrocardiogram about 2 weeks postoperatively, showing low voltage and T-wave changes.

Course in Hospital.—On admission the patient was afebrile, and she remained so throughout the course of hospitalization. The electrocardiogram was within normal limits. Chest x-ray revealed that the lung fields and heart size were entirely within normal limits (Fig. 1). Following completion of medical evaluation, the patient was transferred to the Surgical Service. On Dec. 5, 1956, a total thyroidectomy was performed on the left side and subtotal thyroidectomy on the right side, leaving three parathyroid glands intact. A small portion of the capsule and approximately two grams of thyroid tissue were left. Examination of the tissue revealed that there were several small nodules of thyroid tissue, and on multiple sections, a multinodular gland, with nodules ranging in size from 0.3 to 2.5 cm., was noted. Histologically, the nodules were found to be composed of large follicles with abundant colloid. Some showed small follicles with much pale interfollicular stroma and hemorrhage. Most of the cells showed marked variation of follicular size within the nodule itself. The internodular thyroid tissue was composed of considerable

lymphoid tissue arranged into follicles, and thyroid follicles which contained little colloid and were aligned by large eosinophilic cells. The pathologic diagnoses were (1) nodular goiter and (2) thyroiditis with evident lymphomatosis.

The postoperative course was not remarkable except for some slight induration at the operative site which responded to aspiration and conservative treatment. Approximately 2 weeks postoperatively the patient complained of insidious aching and sharp chest pains, particularly in the right chest, and of some abdominal discomfort which she vaguely described as "indigestion," but which did not respond to the usual symptomatic treatment. There were no associated chills or fever or any generalized aching. There was no history of any pleuritic type of chest pain, no nausea, vomiting, or hematemesis. Physical examination at that time revealed a blood pressure of 126/84 mm. Hg, and there was no obvious distention of the neck veins. There was no demonstrable pulsus paradoxus. The lung fields were clear, and the heart was entirely normal to physical examination. There was no epigastric or abdominal tenderness. The chest x-ray revealed a



A. *B.*

Fig. 3.—*A*, Posteroanterior x-ray of the chest 4 months postoperatively. Cardiac configuration is normal. *B*, Electrocardiogram taken 4 months postoperatively is within normal limits.

definite increase in the transverse cardiac diameter as compared with the initial chest film. The electrocardiogram also revealed circumferential T-wave changes (Fig. 2). A throat culture was negative for hemolytic streptococcus. LE cell preparations were negative on three successive occasions. The white blood cell count was 8,000 with a normal differential; hemoglobin was 14.6 Gm.; hematocrit was 42 per cent. Corrected sedimentation rate was 0. Total cholesterol was 381.4 mg. per cent, cholesterol esters 77 per cent. Serum bilirubin was 0.65. Van den Bergh's direct test was 0.45, indirect was 0.2. Alkaline phosphatase was 3.60 Bodansky units. Total protein was 6.7 Gm., albumin 4.3 Gm., globulin 2.3 Gm. Blood urea nitrogen was 26 mg. per cent. Phosphorus was 29 mEq., sodium 134 mEq., potassium 4.0 mEq., chlorides 107.1 mEq. On Jan. 8, 1957, 33 days postoperatively, the total cholesterol was 471 mg. per cent. On January 10, the protein-bound iodine was 3.3 mcg. per cent. Cardiac fluoroscopy on January 5, revealed a globular cardiac silhouette. There were generalized, markedly decreased pulsations. With the patient in the supine position, there was no widening of the base of the heart. There was increased coarseness of the skin. It was decided to start her on dessicated thyroid. The patient was started on dessicated thyroid, 15 mg. twice daily, on January 10. She was followed with weekly chest x-rays, blood cholesterols, and electrocardiograms. On January 29, for the first time, some decrease in heart size and improvement in the electrocardiogram were noted. On February 4,

chest x-ray revealed an almost complete return of the heart size to normal. A trial of 15 mg. of thyroid three times a day produced considerable substernal discomfort, and return to the twice daily dosage eliminated this complaint. Follow-up studies 4 months postoperatively revealed cholesterol of 300 mg. per cent. The cardiac silhouette and electrocardiogram were now considered normal (Fig. 3).

DISCUSSION

The onset of the myxedematous state in spontaneous hypothyroidism is, for the most part, insidious and gradual. Means[9] cites two cases of "acute" spontaneous myxedema from the literature. Hypothyroidism seldom occurs before the second or third month postoperatively. The unusual aspects of this case are the early onset (about 2 weeks postoperatively) and the development of myxedema initially manifested by an enlarged cardiac silhouette, following which the more pertinent clinical aspects were recognizable.

Postoperative cardiac enlargement, in the absence of underlying heart disease, is rarely observed. Butsch[10] reported two cases of pericarditis, one developing 5 days postoperatively and the other 10 days following surgery. Both procedures were abdominal operations. The etiology of the pericarditis in these cases was obscure. Both patients recovered on a conservative regimen. Spear[11] reported five cases of fibrinous pericarditis occurring in patients subjected to thyroidectomy. Two of these patients had rheumatic heart disease, and the other three had no known cardiac abnormality. It is improbable that these complications represented manifestations of the hypothyroid state. The explanation for the unusually early postoperative development of the myxedematous state in this patient is only speculative. It would appear, from the information available on admission to this hospital, that the patient was euthyroid prior to the institution of thyroid therapy. The protein-bound iodine (7.2 mcg. per cent) and the radioactive iodine uptake (8.1 per cent at the end of 24 hours), determined about 3 to 4 weeks after the administration of thyroid extract was discontinued, were consistent with the usual changes in these indices in euthyroid patients following cessation of dessicated thyroid.[15,17]

Of interest is the fact that preoperatively, almost 2 months after discontinuation of thyroid extract, the patient was still "hypothyroid" from the laboratory standpoint (radioactive iodine uptake 3.2 per cent at the end of 6 hours, and 1 per cent at the end of 24 hours), but, clinically, she appeared euthyroid. Although it has been shown that the majority of euthyroid patients return to normal function within 2 or 3 weeks following cessation of exogenously administered thyroid extract, some may show markedly depressed function for 6 to 11 weeks, without clinically evident hypothyroidism.[16] It would appear, therefore, that the patient was subjected to thyroidectomy during the phase of reduced endogenous thyroid function, brought about through depression of pituitary secretion of thyrotrophin. As indicated, the operation consisted of almost total thyroidectomy, except for about 2.0 Gm. of residual thyroid tissue. As Beierwaltes[15] cautions, evaluation of the status of a thyroid gland following cessation of administration of thyroid extract may be misleading and confusing; nevertheless, one strongly suspects that in this patient ablation of an already depressed gland precipitated myxedema,

which first became clinically evident about 2 or 3 weeks postoperatively. It has been shown that minimal amounts of circulating thyroxine are required to maintain those functions attributed to a viable thyroid gland. The times of appearance of the clinical features of thyroid insufficiency depend on the quantity of functional thyroid tissue available.[12] The stage in which the chemical defects in thyroxine formation occur has been shown to vary in goitrous cretins.[13] Thus, the removal of critical amounts of thyroid tissue in this patient appeared to be sufficient to precipitate myxedema. Further substantiation of this thesis is based on the concept that inadequate amounts of normal hormone may be produced by congenital or acquired defects, and has been re-emphasized by recent studies.[12-14] The possibility also exists that this patient had an acquired intrinsic metabolic defect in her thyroid gland, which was seriously compromised by removal of sufficient hormone-producing tissue to cause the overt hypothyroid state. These suppositions would seem to be supported indirectly by the pathologic findings of marked obliteration and replacement of thyroid tissue by the colloid-poor acini and the excessive amount of lymphoid tissue. It would seem reasonable to assume that the patient was initially euthyroid but required minimal amounts of circulating thyroxine to maintain this state. Following exogenous treatment with dessicated thyroid, laboratory evidence of suppressed function appeared. It was not until subtotal thyroidectomy was performed that the first clinical evidence of myxedema appeared. Following institution of small doses of thyroid extract, the clinically evident myxedematous state and ancillary indices reverted to euthyroid status.

SUMMARY

Presented is a case of myxedema which developed about 2 or 3 weeks post-thyroidectomy in a patient initially euthyroid but rendered "hypothyroid" by the usual laboratory criteria. Clinically evident myxedema, first apparent as cardiopathy, developed only after subtotal thyroid ablation. A review of the literature fails to disclose a similar instance. An attempt is made to explain the dynamics involved.

The clinical and ancillary indices of myxedema were completely reversed by exogenous dessicated thyroid extract.

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Extrathoracic Ectopia Cordis: Report of Cases and Review of Literature

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A recent example of extrathoracic ectopia cordis at Childrens Hospital, and the discovery of an additional case among the hospital records prompted review of the literature and inquiry from other centers in North America and Hawaii. Our present purpose is to summarize this experience briefly, and to review its embryologic and surgical implications.

DISCUSSION

CASE 1.—A Caucasian male infant was admitted to Childrens Hospital on Dec. 17, 1947, at 17½ hours of age, because of extrathoracic ectopia cordis and omphalocele (Fig. 1). The patient was born of a normal pregnancy, 2 weeks prior to the expected date of delivery. Delivery was spontaneous, without complications. Mother and father were 19 and 21 years of age, respectively. Both were living and well. A male sibling, aged 3 years, was healthy.

The patient appeared deeply cyanotic and critically ill. The heart was completely extrathoracic. Its rate was 132 per minute, and it appeared normal in size and configuration. The apex extended toward the right shoulder and was covered with a fibrous membrane. The abdominal portion of the defect protruded about one inch above the surrounding skin. It was soft and compressible, and was thought to contain intestine. The liver was neither visible nor palpable.

The patient was placed in oxygen, but cyanosis was not relieved. The heart was covered with sterile gauze moistened with saline and penicillin. The electrocardiogram showed sinus tachycardia and very low voltage of QRS complexes and T waves in the standard leads. Progressive clinical deterioration occurred, and the patient expired at the age of 8 days.

Autopsy.—On postmortem examination* the heart stood alone outside the left chest. It measured 9 by 4.5 by 3.5 cm. and was covered with yellow-green exudate and fibrin. It was attached to the body only by the large vessels, and lay in a shallow depression in the skin just below the left clavicle. The nipples, sternum, manubrium, and costal cartilages were absent. The thoraco-abdominal mass contained portions of the lungs, diaphragm, liver, gall bladder, stomach, pancreas, small intestine, and colon. The heart demonstrated the tetralogy of Fallot and a widely patent foramen ovale. The lungs showed bronchopneumonia, and blood culture taken at autopsy yielded beta hemolytic streptococcus and gram-negative rods of the paracolon group.

CASE 2.—A Mexican male infant was admitted to Childrens Hospital on Nov. 14, 1957, at 2 hours of age, because of extrathoracic ectopia cordis (Figs. 2 and 3). He was born of an un-

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complicated pregnancy, and was delivered uneventfully at term after labor of 6 to 7 hours' duration. He weighed 7 pounds and 2 ounces. The mother was 18 years of age and unmarried.

On examination the patient appeared well developed, well nourished, and in no distress. Pulse was 92 and respirations 30 per minute. The heart protruded through a defect, 2 by 2 cm., at the xyphocostal notch. At this point the diaphragm was displaced downward, although it was intact throughout. Both atria and ventricles appeared normal. When not under examination, the heart was covered with a dressing moistened with warm normal saline. The examination was otherwise normal except for slight cyanosis of skin and nail beds.

The patient was taken to surgery by Dr. Bertrand Meyer at 5½ hours of age. Under light cyclopropane anesthesia, the sternum was split to the suprasternal notch. The sternum was separated and the surrounding tissue freed from the heart. Repeated attempts to place the heart in the mediastinum consistently resulted in cardiac arrest. The left pleura was opened and the heart was placed in the left pleural space, where it appeared to function satisfactorily. The sternum was approximated with interrupted sutures, and skin and muscles were closed over the defect.

Fig. 1.—Case 1. Extrathoracic ectopia cordis and omphalocele.

At 18 hours of age the patient appeared minimally cyanotic, and respirations were somewhat labored. By age 24 hours cyanosis had increased, respirations were shallow, and the pulse had risen to 180 per minute. The patient appeared to improve when 100 per cent oxygen was given by mask, although he was somewhat cyanotic in 50 per cent oxygen. At age 33 hours a sudden episode of apnea, cyanosis, and pronounced bradycardia improved after the injection of aqueous Adrenalin 1:1,000 (0.1 c.c.) and caffeine with sodium benzoate (0.25 c.c.). The period of apnea lasted from 2 to 3 minutes. X-ray of the chest at this time showed good aeration of the right lung and partial pneumothorax on the left. Moist râles were noted bilaterally. At age 52½ hours the infant again became apneic, and the heart beat ceased. He failed to respond to the intracardiac injection of Adrenalin or to artificial respiration.

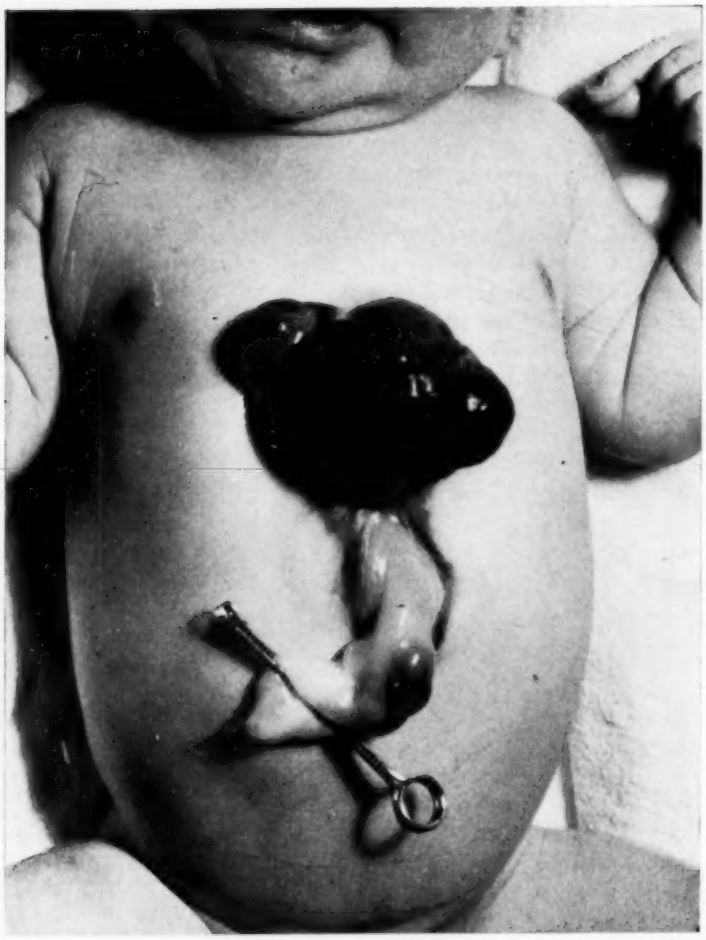

Fig. 2.—Case 2. Extrathoracic ectopia cordis, frontal aspect.

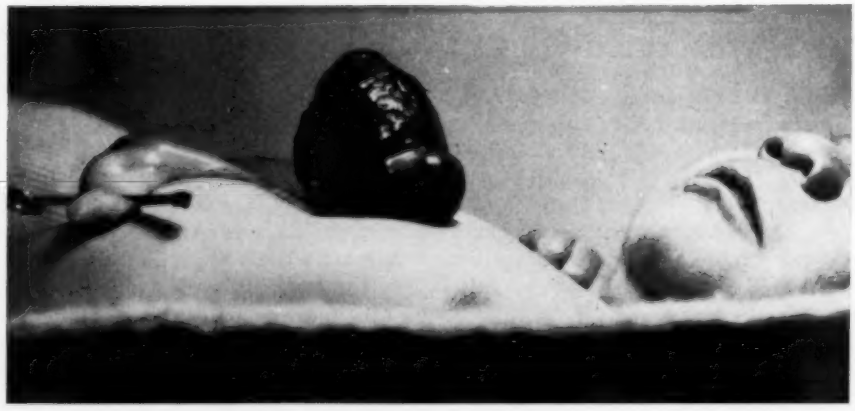

Fig. 3.—Case 2. Extrathoracic ectopia cordis, left lateral aspect.

Autopsy.—Postmortem examination* showed that the heart lay transversely in the left pleural cavity between the lobes of the left lung. There was no parietal pericardium. There was no apparent obstruction to inflow from the venae cavae. A persistent left superior vena cava entered the right atrium via the coronary sinus. The foramen ovale was patent, and there was a large (1.3 cm. in diameter) patent ductus arteriosus. All major vessels appeared normal, although unusually long. No anatomic obstruction to cardiac inflow or outflow could be demonstrated. However, it was possible to cause obstruction of various vessels by moving the heart, and it was postulated that movement of the child with respiration or in handling might have caused significant antemortem vascular obstruction. The lungs showed considerable congestion, and a large amount of thin, frothy material was noted in bronchi and bronchioles. The liver weighed 103 grams (normal 78 grams), but showed no other abnormality. The right ureter was moderately dilated in its proximal two thirds.

DISCUSSION

Review of Literature.—The first recorded case of ectopia cordis is generally attributed to Haller or Martinez, in 1706.[2-4] In 1671-1672, however, Niels Stensen (Nicholas Steno) described the first case of tetralogy of Fallot.[1] This case is also the first reported example of extrathoracic ectopia cordis.

In all, we have found 45 cases of extrathoracic ectopia cordis in the literature. By personal communication we have added 5, for a total of 50 cases. Seventeen were known to be male, and 14 were female. Thirteen were described as premature, and 18 were full term. Five were stillborn. Untoward events or noxious influences during pregnancy were not reported, with the single exception of an attempted self-abortion mentioned by Lintgen.[18] The patient who survived the longest was the one reported by Sweet and Parks,[30] who lived 3 weeks. Rolland's case[12] was one of twins, the other of whom appeared normal but died of prematurity. No other twins are reported. Surgery was attempted in 9 cases, without apparent effect on survival. Seventeen cases were found to have associated cardiac defects, and 4 of the hearts were normal except for the malposition. Ventricular septal defect was the most frequently associated cardiac anomaly. Noncardiac congenital abnormalities, of which cleft lip and/or cleft palate were most common, were present in 21 of the 27 cases in which mention was made of other anomalies. Among other mammalian and avian species, ectopia cordis has been reported in the dog, lamb, calf, pigeon, and orangutan.[5]

Embryology.—Patten[37] states that mid-ventral structures appear first on either side of the midline and converge toward it as development progresses. He believes that the defect of ectopia cordis must be established about the third week of development. He states, "It is at this time that the demarcation between intra- and extra-embryonic coelom is being established by the folding off of the body. When the ventral body walls in the cardiac region are being formed, they must catch the heart outside their place of convergence rather than inside as occurs normally. Whether the primary disturbance is something which causes the heart to protrude abnormally far ventrally, or whether it has something to do with the growth pattern of the body walls is difficult to guess." Taussig[38] notes: "Ectopia cordis represents an arrest in the development of the heart of such a nature that it fails to complete its descent into the thorax."

*Dr. R. Cleland, pathologist.

TABLE I. CASES OF EXTRATHORACIC ECTOPIA CORDIS REPORTED IN THE WORLD LITERATURE, 1671-1957, INCLUDING 5 CASES REPORTED TO THE AUTHORS BY PERSONAL COMMUNICATION

REFERENCE	AUTHOR	DATE	SEX	GESTATION AGE	SURGERY	CARDIAC ANOMALIES	NONCARDIAC ANOMALIES
1	Stenson	1671	U	U	O	Tetralogy of Fallot	P
2 (3, 4)	Haller (Martinez)	1706	M	U	O	A	U
3, 4	Breschet	1745	F	U	O	IVSD, 2 superior venae cavae, Overriding aorta	U
2, 4	Morand	1759	U	U	O	U	U
2, 5	Sandifort	1772	F	U	O	A	A
3	Tourtelle	1784	U	P	O	U	U
3, 5	Walter	1805	U	T	O	IVSD, 2 superior venae cavae	U
2, 3, 4	Cruvelhier	1841	U	U	O	U	U
5	Jones	1855	M	P	O	U	U
2, 3, 4	Daniell	1860	U	T	O	IVSD	U
2, 4	O'Connor	1861	M	P	O	U	P
2	Ranvier	1863	M	P	O	U	U
6	Schlesinger	1870	U	U	O	IVSD, 2 superior venae cavae	U
2, 4	Braun-Fernwald	1894	U	U	O	U	P
6(2,3,7)	Grant (Barnardo)	1896	F	P	O	U	A
8	Lilwall-Cormac	1903	F	T	O	U	P
9	Goode	1903	F	T	O	U	U
10	Ellis	1906	M	T	O	U	U
11	Greiffenberg	1908	F	U	O	IVSD, 2 superior venae cavae	P
2	Birnbaum	1912	M	P, S	O	U	U
12	Rolland	1913	M	P, S	O	A	A
13	Cosgrove and St. George	1924	M	P, S	O	2 superior venae cavae	P
14	Cutler and Wilens	1925	M	T	X	Absent inferior venae cava, Stenosis of aortic isthmus	P
15	Bloch	1927	M	T	X	U	U
16	Stiemens	1929	M	U	O	U	P
17	Wedd	1929	U	T	X	U	U
18	Lintgen	1932	U	U	O	U	P
19	Heijl	1932	F	T	O	U	P
2	Trillat	1934	F	P	O	U	U
2, 3	Ledenyi	1935	U	T, S	O	U	P
20	Potter	Approx. 1935	U	U	O	U	U
3	Kellett	1936	M	T	O	Incomplete development of atrial and ventricular septa	P
21	Wanstrom	1936	M	P, S	O	U	P
22	Vaysierre and Michotey	1937	M	P	O	U	A
23	Barlow	1938	F	P	O	Absent right atrium	P
24	Puddu and Cammarella	1938	M	U	O	U	P
25	Kühnel	1940	U	U	O	U	U
26	Sosyal	1940	U	U	O	U	U
26	Finocchietto	?	U	U	X	U	U
27	George	1945	U	T	O	U	P
28	Taussig	Approx. 1946	U	U	O	Grossly malformed	U
26	Byron	1947	F	T	X	Tetralogy of Fallot	P
29	Feeney	1950	U	T	X	IVSD, Aortic displacement	P
30	Sweet and Parks	1952	U	U	O	U	P
31	Becker	1952	M	P	X	IVSD, Transposition of aorta	A
32	Univ. of Wisconsin Hospitals	1953	M	T	X	Pulmonary stenosis, Absent pulmonary venous drainage	U
33	Saxen and Kinnunen	1954	F	T	O	IVSD, IASD	A
34	John Gaston Hosp., Memphis, Tenn.	1954	F	U	X	U	U
35	Dominiczac	1956	F	T	O	A	P
36	Steiner-Pritzker	1956	F	T	O	Tricuspid atresia, IVSD, IASD, Hypoplasia right ventricle and pulmonary artery	P

Sex: M = Male. F = Female. U = Unknown.
Gestation age: P = Premature. T = Term. S = Stillborn. U = Unknown.
Surgery: O = Surgery not done. X = Surgery performed.
Cardiac anomalies: A = Absent. U = Unknown.
Noncardiac Anomalies: A = Absent. P = Present. U = Unknown.

Surgery.—Surgical attempts to correct extrathoracic ectopia cordis have been entirely unsuccessful, although other types of ectopia cordis have been operated successfully. The usual surgical problems include the following considerations: (1) intrathoracic space for the heart, (2) angulation of vessels with embarrassment of the cardiac action, and (3) absence of normal skin beneath the heart in some cases.[26] If the mediastinum offers too little space for the heart, the left pleural space may be utilized, and left lower lobectomy may be considered if necessary.* Angulation of vessels appears to be the major problem, particularly to the extent that it obstructs cardiac inflow. It is essential that the heart be placed and maintained in a satisfactory position. Supporting structures are not available, and pericardium is often absent, making firm fixation of the heart difficult or impossible. Angulation may be further minimized if the great vessels are dissected as free as possible. Defective skin, if present, is roughly the shape of the heart. Barlow[23] suggested that it is "presumably caused during intrauterine life by friction of the heart beat." In such cases, a partial skin flap over the heart does not appear to be therapeutically satisfactory.

TABLE II. VITAL DATA FROM 52 REPORTED CASES OF EXTRATHORACIC ECTOPIA CORDIS, INCLUDING 2 CASES IN THE PRESENT REPORT

Sex:		*Additional cardiac abnormalities:*	
Male	19	Present	19
Female	14	Absent	4
Unknown	19	Unknown	29
Gestational age and stillbirths:		*Other noncardiac abnormalities:*	
Premature	14	Present	22
Term	19	Absent	7
Unknown	19	Unknown	23
Stillborn	5		
Surgery attempted:	10		
Survival:	0		

Special attention to general supportive care is important, as in any surgical procedure at this age. It may be wise to delay surgery until approximately 48 hours of age, in order to allow pulmonary physiology and other homeostatic mechanisms to become stabilized. During this period the heart should be protected externally, and moisture, antibiotics, and warmth should be provided.

SUMMARY

We have reported and reviewed only extrathoracic ectopia cordis. Two major criteria for this diagnosis have been employed: (1) that the heart be truly extrathoracic, not merely part of a herniation, although herniation below the

*Making room for the heart in the left pleural space by left lower lobectomy has not been attempted in the reported cases. It was suggested as a possible approach by Dr. Bertrand W. Meyer, of the Thoracic Surgical Service.

extrathoracic heart may be found coincidentally; and (2) that the heart remain above the diaphragm, not passing through a diaphragmatic defect. The two cases presented fulfill these criteria.

In the reported cases, pregnancy is almost uniformly uneventful. The incidence of prematurity is greater with ectopia cordis than in the general population, although more term babies exhibit the abnormality. Males are affected slightly more often than females. Associated cardiac anomalies are found in the majority. Other congenital malformations are common, although they are not usually lethal in themselves.

Despite consistent surgical failure, it is recognized that survival is impossible without surgical correction. Surgical repair should be attempted in all such cases in the hope that accumulating experience will permit survival.

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Book Review

HANDBOOK OF RESPIRATION. Compiled by Philip L. Altman, John F. Gibson, and Charles C. Wang, Philadelphia and London, W. B. Saunders Company.

This handbook was prepared under the direction of the Committee on the Handbook of Biological Data, The National Academy of Sciences and National Research Council in the United States. It contains nearly 400 pages of information relevant to every aspect of respiratory physiology. Most of the data is in the form of tables. These enable relevant information to be sought and found quickly, and are of great service to those working in the field by giving them a quick source of reference on any particular topic. The information has been carefully compiled and appears to this reviewer to be reasonably comprehensive; the only deficiency is that in some of the tables insufficient information is given about methods used by the authors being quoted, and this makes it difficult for the reader to form a judgment of the significance of some of the variations reported. A particular instance of this is the table dealing with lung volumes, in which the posture of the experimental subjects is not mentioned. This makes comparison between the different sets of data difficult. However, this is a minor point of criticism in a most useful compilation of information.

The reviewer could think of no aspect of respiratory physiology that does not receive at least a mention in this handbook, and a great deal of the collected data on respiration is extremely valuable to have. One section which has been excellently compiled and set out is that dealing with the effects of drugs on the respiratory system, and the reported results of the administration of many hundreds of compounds are tabulated here together with the sources of information, so that the reader is able quickly to find the information he is seeking. This handbook may be regarded as an essential addition to every reference library, and individual workers associated with the respiratory field will undoubtedly find it a most useful volume to have on their shelves.

D. V. B.

Announcements

The American Heart Association and the United States Public Health Service has issued a joint statement recommending that persons with heart and blood vessel disease obtain vaccinations against influenza.

The statement pointed out that the dangers of influenza are greater for patients with heart or lung disease than for others, and that the risk is particularly great among people with lung congestion due to heart disease.

It was also emphasized that influenza vaccinations, which have been shown in epidemic areas to be effective in helping prevent the infection or in reducing its severity, do not produce local or general reactions that would be significantly hazardous to people with heart conditions. Vaccination is contraindicated only for those who have an allergy to eggs.

In releasing the statement, Dr. Leroy E. Burney, Surgeon General of the Public Health Service, and Dr. Francis L. Chamberlain, President of the American Heart Association, said,

"Influenza can be a real threat to the cardiac. It is frequently a serious illness in this group and may result in death. It is urged that all heart patients take steps to obtain the protection that vaccination will give." The complete text of the joint statement follows:

"Experience has shown that patients with heart or lung diseases are more susceptible to the hazards of influenza than is the general population. This increased risk is shown by more severe illness and by higher case fatality rates among patients with these diseases. Patients with, or prone to, pulmonary congestion secondary to heart disease are an especially high risk group.

"Studies with influenzal vaccine have clearly shown that its use significantly reduces the incidence and probably the severity of influenzal infection, in the presence of local or widespread epidemics. Furthermore, use of the vaccine is contraindicated only in those patients who are allergic to the components of the vaccine. The type of local and systemic reactions to vaccine have not been such as to constitute any significant hazard to patients with cardiac disease.

"Therefore, the American Heart Association and the Public Health Service, through its National Heart Institute, recommend that all persons with cardiovascular disease seek the benefit of protection which is afforded by the proper use of polyvalent influenzal vaccine."

The University of Minnesota announces a CONTINUATION COURSE IN INTERNAL MEDICINE FOR INTERNISTS to be held at the Center for Continuation Study on the university campus from March 16 to 18, 1959. The areas to be covered this year include diseases of the kidney and gastrointestinal tract, chemotherapy of cancer, and clinical uses of steroids.

Guest speakers will include Dr. Robert M. Kark, Professor of Medicine, University of Illinois College of Medicine, Chicago, Ill.; Dr. Joseph B. Kirsner, Professor of Medicine, University of Chicago School of Medicine, Chicago, Ill.; and Dr. Richard T. Smith, Rheumatologist, Philadelphia, Pa. The remainder of the faculty will include members of the faculties of the University of Minnesota School of Medicine and the Mayo Foundation. The course will be presented under the direction of Dr. Wesley W. Spink, Professor, Department of Medicine.